STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 133033

TO: Shahnam J Sharareh **Location: 4c25 / 4b18** **Wednesday, September 22, 2004** **Art Unit: 1617** **Phone: 272-0630** **Serial Number: 09 / 912609**	**From: Jan Delaval** **Location: Biotech-Chem Library** **Rem 1A51** **Phone: 272-2504** **jan.delaval@uspto.gov**

Search Notes

STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 133188

TO: Shahnam J Sharareh **Location: 4c25 / 4b18** **Wednesday, September 22, 2004** **Art Unit: 1617** **Phone: 272-0630** **Serial Number: 09 / 912609**	**From: Jan Delaval** **Location: Biotech-Chem Library** **Rem 1A51** **Phone: 272-2504** **jan.delaval@uspto.gov**

Search Notes

STIC-Biotech/ChemLib 133033 + 133188

From: Unknown@Unknown.com
Sent: Monday, September 20, 2004 2:31 PM
To: STIC-Biotech/ChemLib
Subject: Generic form response

ResponseHeader=Commercial Database Search Request

AccessDB#= _____

LogNumber= _____

Searcher= _____

SearcherPhone= _____

SearcherBranch= _____

MyDate=Mon Sep 20 14:31:29 EDT 2004

submitto=Biotech01@uspto.gov

Name=Shahnam Sharareh

Empno=76656

Phone=20630

Artunit=1617

Office=4C25 Rem

Serialnum=09912609

PatClass=424/9.5-9.52

Earliest=2001

Format1=paper

Format3=email

Searchtopic=Attention: Jan Delavel.

Please search for a pharmaceutical composition comprising
(a) a copolymer of polycaprolactone and polyethylene glycol
(b) a drug, selected species: camptothecin
(c) a targeting ligand of SEQ ID 9. Which is CRGDC.

(preferably with the targeting ligand attached to the polymer via a covalent bond, otherwise not important)
Please also do a search on the SEQ ID 9. and the polymer itself without the drug.

****
STAFF USE ONLY
Searcher: Jan
Searcher Phone: 2-2504
Date Searcher Picked up: 9/22
Date Completed: 9/22
Searcher Prep/Rev. Time: 20
Online Time: 90

****
Type of Search
NA Sequence: #_____
AA Sequence :# ✓
Structure: # ✓
Bibliographic: _____
Litigation: _____
Patent Family: _____
Other: _____

****
Vendors and cost where applicable
STN: ✓
DIALOG: _____
QUESTEL/ORBIT: _____
LEXIS/NEXIS: _____
SEQUENCE SYSTEM: ✓
WWW/Internet: _____
Other(Specify): _____

Please also do an inventor search.Inventors are: Evan Unger, Terry Matsunaga, Varadarajan Ramaswami, Marek Romanowski.

The Assignee is IMrax.

thanks.
Shahnam Sharareh, AU 1617

Comments=

send=SEND

****
STAFF USE ONLY

Searcher:_____
Searcher Phone: 2-
Date Searcher Picked up:____
Date Completed:_____
Searcher Prep/Rev. Time:___
Online Time:_____

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Type of Search
NA Sequence: #_____
AA Sequence :#_____
Structure: #_____
Bibliographic:_____
Litigation:_____
Patent Family:_____
Other:_____

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Vendors and cost where applicable
STN:_____
DIALOG:_____
QUESTEL/ORBIT:_____
LEXIS/NEXIS:_____
SEQUENCE SYSTEM:_____
WWW/Internet:_____
Other(Specify):_____

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=> d his

     (FILE 'HOME' ENTERED AT 06:36:24 ON 22 SEP 2004)
               SET COST OFF

     FILE 'REGISTRY' ENTERED AT 06:36:36 ON 22 SEP 2004
               E CRGDC/SQEP
L1           28 S E3
               E CAMPTOTHECIN/CN
L2            1 S E3
L3           59 S C20H16N2O4/MF AND 5/NR
L4           15 S L3 AND 7726/RID
L5            3 S L4 NOT (LABELED OR (T OR D)/ELS OR 9 HYDROXY)
L6            3 S L2,L5
               SEL RN
L7           10 S E1-E3/CRN
L8            1 S L7 AND NA/ELS
L9            4 S L6,L8
L10           1 S 502-44-3
L11        5603 S 502-44-3/CRN
L12         566 S L11 AND C2H4O
L13          43 S L12 AND 2/NC
L14           6 S L13 AND OC2/ES
               SEL RN 2 4
L15           4 S L14 NOT E4-E5
L16          37 S L13 NOT L14
L17           4 S L16 AND 25322-68-3/CRN
L18           4 S L17 AND 2/NC
               SEL RN 1 2
L19           2 S L18 NOT E6-E7
L20         169 S L12 AND 25322-68-3/CRN NOT L17
L21           1 S L20 AND NA/ELS AND 3/NC
L22         222 S L12 AND 75-21-8/CRN
L23         218 S L22 NOT L13
L24          94 S L23 NOT (N OR S OR P OR SI)/ELS
L25           1 S L11 AND 1/NC
L26           1 S 25248-42-4
L27          25 S 25248-42-4/CRN
L28           1 S L27 AND LI/ELS
L29           1 S L27 AND HEXANOIC
L30           1 S 142-62-1
L31          18 S 142-62-1/CRN AND C2H4O
L32           3 S L31 AND 2/NC
L33           1 S 68993-43-1
L34          93 S 142-62-1/CRN AND PMS/CI
L35           5 S L34 AND 1/NC
L36           1 S 115489-47-9
L37           4 S L25,L26,L28,L36
L38         616 S L11 AND HOMOPOLYMER
L39         384 S L38 NOT (N OR SI OR S OR P OR CL OR BR OR F OR I)/ELS
L40         174 S L39 NOT (COMPD OR WITH OR UNSPECIFIED)
L41         103 S L40 AND 1/NR
L42           3 S L41 AND SALT
L43           2 S L42 AND LI/ELS
L44           1 S L43 AND 2/NC
L45           5 S L37,L44
L46           1 S 25322-68-3

     FILE 'HCAPLUS' ENTERED AT 07:03:25 ON 22 SEP 2004
L47        2556 S L9
L48        4375 S ?CAMPTOTHECIN? OR NSC94600 OR NSC302991  OR NSC()(94600 OR 94
L49        4401 S L47,L48
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                E 7726/RID
L50          3982 S E82
L51          3978 S L50 NOT L9

     FILE 'HCAPLUS' ENTERED AT 07:05:55 ON 22 SEP 2004
L52          3356 S L51
L53            29 S L1
L54             7 S CRGDC
L55            23 S ?CRGDC?
L56             1 S L49 AND L53-L55
L57             0 S L52 AND L53-L55
L58           216 S L15,L19,L21,L33
L59             0 S L58 AND L56
L60             3 S L58 AND L49,L52
L61             0 S L58 AND L53-L55
L62          7576 S L45
L63          9604 S ?POLYCAPROLACTON? OR POLY CAPROLACTON? OR POLY EPSILON CAPROL
L64         10471 S L62,L63
L65            22 S L64 AND L49,L52
L66             1 S L64 AND L53-L55
L67         76643 S L46
L68         79256 S PEG OR POLYETHYLENEGLYCOL OR POLYETHYELENEOXIDE OR POLYOXYETH
L69           304 S POLY() (ETHYLENEGLYCOL OR ETHYELENEOXIDE)
L70         23999 S POLY()ETHYLENE() (GLYCOL OR OXIDE)
L71         97747 S POLYETHYLENE() (GLYCOL OR OXIDE)
L72          8093 S POLYOXY ETHYLENE OR POLY() (OXYETHYLENE OR OXY ETHYLENE)
L73        175992 S ETHYLENEGLYCOL OR ETHYLENEOXIDE OR ETHYLENE() (GLYCOL OR OXIDE
L74         67705 S POLYOXYALKYLENE#/CW
L75           249 S L49,L52 AND L67-L74
L76             4 S L53-L55 AND L67-L74
L77            26 S L56,L60,L65,L66,L76
L78            16 S L75 AND L77
L79            26 S L77,L78
                E IMARX/PA,CS
                E IMAR/PA,CS
L80             1 S E16-E19
L81            60 S E43-E66
                E UNGER E/AU
L82           208 S E3,E4,E42-E44
                E MATSUNAGA T/AU
L83           151 S E3,E5
                E MATSUNAGA TERRY/AU
L84            54 S E3-E5
                E RAMASWAMI V/AU
L85            30 S E3,E4
                E ROMANOWSKI M/AU
L86            21 S E3,E5,E6
L87             5 S L80-L86 AND L49,L52
L88             1 S L80-L86 AND L53-L55
L89             5 S L87,L88
L90             2 S L89 AND L79
L91             1 S EP98-921109/AP,PRN
L92             6 S L89,L90,L91
L93            24 S L79 NOT L92
L94             4 S L56,L66,L76
                SEL DN AN 3
L95             1 S E1-E3 AND L94
L96             1 S L66 AND L76
L97             6 S L92,L95,L96
L98             3 S L94 NOT L97

     FILE 'HCAPLUS' ENTERED AT 07:27:05 ON 22 SEP 2004
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L99           6 S L97 AND L47-L49,L52-L98
L100          3 S L98 AND L47-L49,L52-L99

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 07:28:27 ON 22 SEP 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 22 Sep 2004  VOL 141 ISS 13
FILE LAST UPDATED: 21 Sep 2004  (20040921/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> d l99 all hitstr tot

L99  ANSWER 1 OF 6  HCAPLUS  COPYRIGHT 2004 ACS on STN
AN   2004:39613  HCAPLUS
DN   140:117375
ED   Entered STN:  16 Jan 2004
TI   Stabilized nanoparticle formulations of camptothecin derivatives
IN   Unger, Evan Charles; Romanowski, Marek J.;
     Ramaswami, Varadarajan; Zutshi, Reena; Labell, Rachel Yvonne;
     Pigman, Elizabeth Anne
PA   USA
SO   U.S. Pat. Appl. Publ., 27 pp., Cont.-in-part of U.S. Ser. No. 165,867.
     CODEN: USXXCO
DT   Patent
LA   English
IC   ICM  A61K031-4745
     ICS  A61K009-14
NCL  424486000; 514283000
CC   63-6 (Pharmaceuticals)
     Section cross-reference(s): 1
FAN.CNT 7
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
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PI   US 2004009229        A1    20040115    US 2003-457068          20030605
     US 2002041898        A1    20020411    US 2001-912609          20010725
     US 2003059465        A1    20030327    US 2002-165867          20020606
PRAI US 2000-478124       A2    20000105
     US 2000-703484       A2    20001031
     US 2001-912609       A2    20010725
     US 2002-165867       A2    20020606
     US 1998-75477        A2    19980511
     US 2000-703474       A2    20001031
CLASS
 PATENT NO.       CLASS  PATENT FAMILY CLASSIFICATION CODES
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 US 2004009229    ICM    A61K031-4745
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ICS A61K009-14
NCL 424486000; 514283000
US 2003059465 ECLA A61K009/107D; A61K009/51; A61K047/48W18B; A61K047/48W18; A61L029/16; A61L031/16

OS MARPAT 140:117375

AB Pharmaceutical formulations are provided that increase the systemic bioavailability of **camptothecin** derivs.; preferably, the **camptothecin** derivative is 7-ethyl-10-hydroxyl **camptothecin**, SN-38. The drug is complexed with a stabilizing agent, but is not covalently bound thereto. Anionic or neutral lipids and/or polymers are used as the stabilizing agent, and secondary stabilizing agents and/or other excipients may be incorporated into the formulation as well. Therapeutic methods are also provided, wherein a formulation of the invention is administered to a patient to treat a condition, disorder, or disease that is responsive to **camptothecin** derivs. Generally, administration is oral or parenteral.

ST **camptothecin** deriv nanoparticle formulation

IT Polymers, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(block, stabilizing agents; stabilized nanoparticle formulations of **camptothecin** derivs.)

IT Drug delivery systems
(freeze-dried; stabilized nanoparticle formulations of **camptothecin** derivs.)

IT Drug delivery systems
(nanoparticles; stabilized nanoparticle formulations of **camptothecin** derivs.)

IT Drug delivery systems
(parenterals; stabilized nanoparticle formulations of **camptothecin** derivs.)

IT Drying
(spray; stabilized nanoparticle formulations of **camptothecin** derivs.)

IT Antitumor agents
Human
Molecular weight distribution
Stabilizing agents
(stabilized nanoparticle formulations of **camptothecin** derivs.)

IT **Polyoxyalkylenes**, biological studies
RL: MOA (Modifier or additive use); POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilizing agent; stabilized nanoparticle formulations of **camptothecin** derivs.)

IT Phosphatidylcholines, biological studies
Phosphatidylinositols
Phosphatidylserines
Phospholipids, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilizing agent; stabilized nanoparticle formulations of **camptothecin** derivs.)

IT Dendritic polymers
RL: MOA (Modifier or additive use); POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilizing agents; stabilized nanoparticle formulations of **camptothecin** derivs.)

IT Lipids, biological studies
Phosphatidylethanolamines, biological studies
Polymers, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(stabilizing agents; stabilized nanoparticle formulations of **camptothecin** derivs.)

IT 81490-05-3, Palmitoyloleoyl phosphatidylglycerol 214334-87-9, Dioleoyl phosphatidylglycerol
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilized nanoparticle formulations of **camptothecin** derivs.)

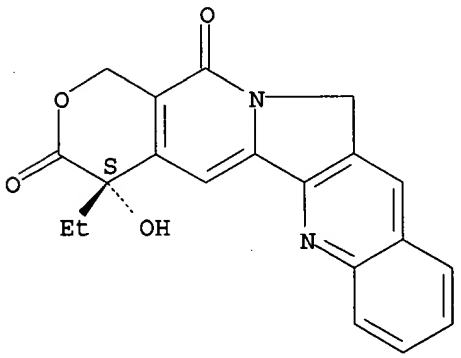
IT **7689-03-4D**, **Camptothecin**, analogs **86639-52-3**, Sn-38
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(stabilized nanoparticle formulations of **camptothecin** derivs.)

IT 9002-89-5, Polyvinyl alcohol 9003-39-8, Polyvinyl pyrrolidone **24980-41-4**, **Polycaprolactone 25248-42-4**, **Polycaprolactone 25322-68-3**, **Polyethylene glycol** 26009-03-0, Polyglycolide 26202-08-4, Polyglycolide 26780-50-7, Poly(lactide-co-glycolide) 31694-55-0 53694-15-8 61931-73-5 88306-52-9 88306-53-0 106392-12-5 110617-70-4, Poloxamine **120619-61-6**
RL: MOA (Modifier or additive use); POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilizing agent; stabilized nanoparticle formulations of **camptothecin** derivs.)

IT **7689-03-4D**, **Camptothecin**, analogs **86639-52-3**, Sn-38
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(stabilized nanoparticle formulations of **camptothecin** derivs.)

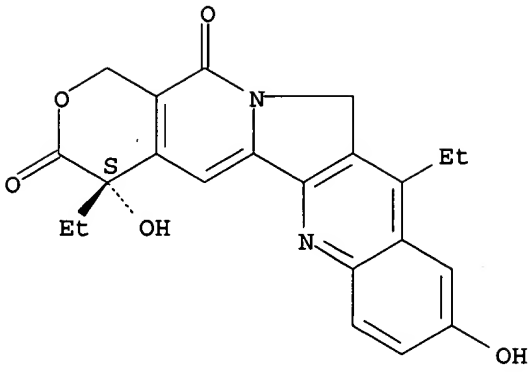
RN 7689-03-4 HCAPLUS
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 4-ethyl-4-hydroxy-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 86639-52-3 HCAPLUS
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 4,11-diethyl-4,9-dihydroxy-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

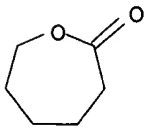


IT **24980-41-4, Polycaprolactone 25248-42-4, Polycaprolactone 25322-68-3, Polyethylene glycol 120619-61-6**
RL: MOA (Modifier or additive use); POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilizing agent; stabilized nanoparticle formulations of **camptothecin** derivs.)

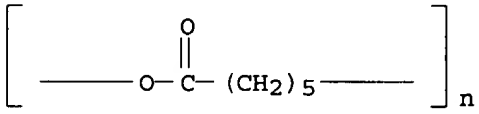
RN 24980-41-4 HCAPLUS
CN 2-Oxepanone, homopolymer (9CI) (CA INDEX NAME)

CM 1

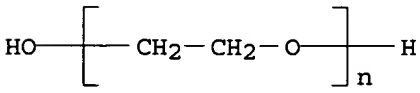
CRN 502-44-3
CMF C6 H10 O2



RN 25248-42-4 HCAPLUS
CN Poly[oxy(1-oxo-1,6-hexanediyl)] (9CI) (CA INDEX NAME)



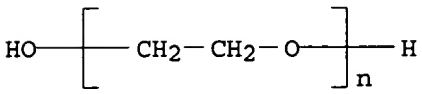
RN 25322-68-3 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



RN 120619-61-6 HCAPLUS
CN 2-Oxepanone, polymer with α-hydro-ω-hydroxypoly(oxy-1,2-ethanediyl), block (9CI) (CA INDEX NAME)

CM 1

CRN 25322-68-3
CMF (C2 H4 O)n H2 O
CCI PMS



CM 2

CRN 502-44-3
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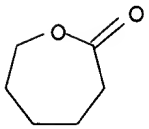


L99 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:640795 HCAPLUS
DN 140:223023
ED Entered STN: 18 Aug 2003
TI Nanoparticle drug delivery system for intravenous delivery of topoisomerase inhibitors
AU Williams, Joshua; Lansdown, Rachael; Sweitzer, Robert; **Romanowski, Marek**; LaBell, Rachel; Ramaswami, Rajan; **Unger, Evan**
CS **ImaRx Therapeutics, Inc., Tucson, AZ, 85719, USA**
SO Journal of Controlled Release (2003), 91(1-2), 167-172
CODEN: JCREEC; ISSN: 0168-3659
PB Elsevier Science Ltd.
DT Journal
LA English
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1
AB **Camptothecin**-based drugs, because of their poor solubility and labile lactone ring, pose challenges for drug delivery. The purpose of this research was to develop a nanoparticle delivery system for camptotheca alkaloids. After initial investigations SN-38 was selected as the candidate camptotheca alkaloid for further development. Nanoparticles comprising SN-38, phospholipids and **polyethylene glycol** were developed and studied in vitro and in vivo. The SN-38 formulations were stable in human serum albumin and high lactone concns. were observed even after 3 h. In vivo studies in nude mice showed prolonged half-life of the active (lactone form) drug in whole blood and increased efficacy compared to Camptosar in a mouse xenograft tumor model.
ST nanoparticle drug delivery system topoisomerase inhibitor
IT Drug bioavailability
Human
Particle size
Stability
(nanoparticle drug delivery system for i.v. delivery of topoisomerase inhibitors)
IT Phospholipids, biological studies
Polyoxyalkylenes, biological studies

RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nanoparticle drug delivery system for i.v. delivery of topoisomerase inhibitors)

IT Drug delivery systems
(nanoparticles; nanoparticle drug delivery system for i.v. delivery of topoisomerase inhibitors)

IT Albumins, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(serum; nanoparticle drug delivery system for i.v. delivery of topoisomerase inhibitors)

IT 80449-01-0, Topoisomerase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; nanoparticle drug delivery system for i.v. delivery of topoisomerase inhibitors)

IT **25322-68-3, Polyethylene glycol**
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nanoparticle drug delivery system for i.v. delivery of topoisomerase inhibitors)

IT **7689-03-4, Camptothecin 86639-52-3**, SN-38
97682-44-5, Irinotecan
RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(nanoparticle drug delivery system for i.v. delivery of topoisomerase inhibitors)

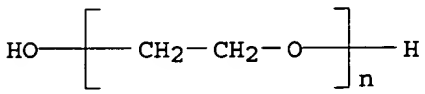
RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Chow, D; Ann NY Acad Sci 2000, V922, P151
(2) Cortesi, R; Pharm Sci Technol Today 1999, V2(7), P288 HCAPLUS
(3) Creaven, P; Cancer Chemother Rep 1973, V57, P175 MEDLINE
(4) Emerson, D; Pharm Sci Technol Today 2000, V3(6), P205 HCAPLUS
(5) Garcia-Carbonero, R; Clin Cancer Res 2002, V8, P641 HCAPLUS
(6) Gottlieb, J; Cancer Chemother Rep 1970, V54, P461 HCAPLUS
(7) Kaneda, N; Cancer Res 1990, V50, P1715 HCAPLUS
(8) Mathijssen, R; Clin Cancer Res 2001, V7, P2182 HCAPLUS
(9) Slichenmyer, W; J Natl Cancer Inst 1993, V85, P271 HCAPLUS
(10) Takimoto, C; Cancer Chemotherapy and Biotherapy:Principles and Practice, 3rd Edition 2001, P579
(11) Warner, D; J Chromatogr B 1997, V691, P161 HCAPLUS

IT **25322-68-3, Polyethylene glycol**
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nanoparticle drug delivery system for i.v. delivery of topoisomerase inhibitors)

RN 25322-68-3 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)

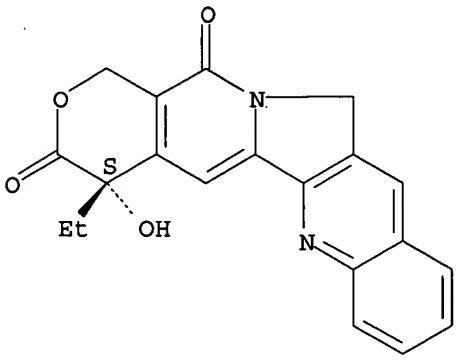


IT **7689-03-4, Camptothecin 86639-52-3**, SN-38
97682-44-5, Irinotecan
RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(nanoparticle drug delivery system for i.v. delivery of topoisomerase inhibitors)

RN 7689-03-4 HCAPLUS
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione,

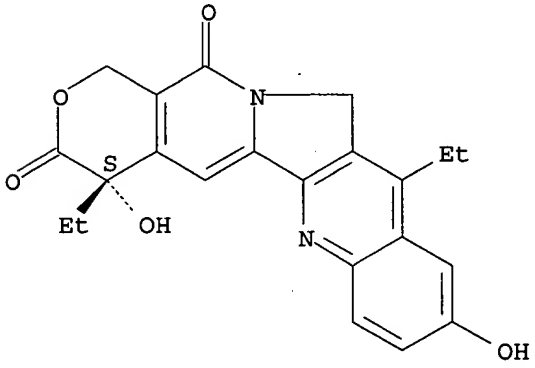
4-ethyl-4-hydroxy-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



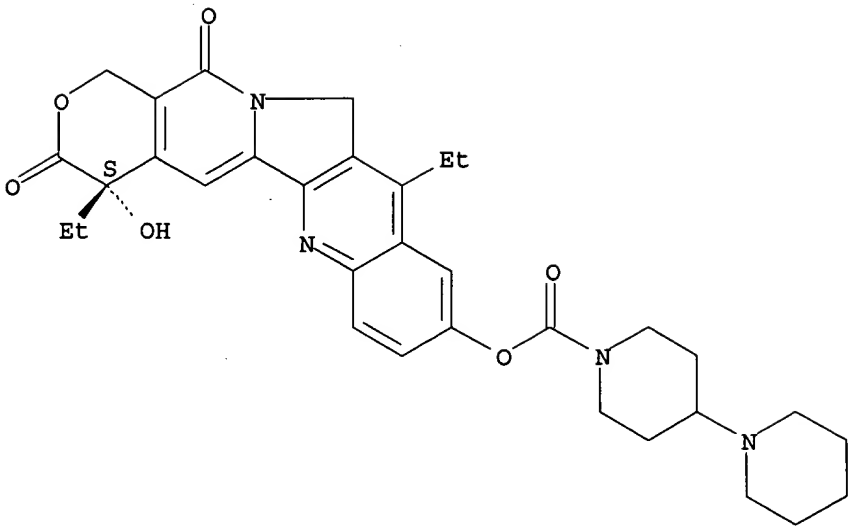
RN 86639-52-3 HCAPLUS
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 4,11-diethyl-4,9-dihydroxy-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 97682-44-5 HCAPLUS
CN [1,4'-Bipiperidine]-1'-carboxylic acid, (4S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L99 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:241779 HCAPLUS
DN 138:260458
ED Entered STN: 28 Mar 2003
TI Stabilized nanoparticle formulations of Camptotheca compounds
IN **Unger, Evan C.; Romanowski, Marek J.; Ramaswami, Varadarajan**
PA USA
SO U.S. Pat. Appl. Publ., 22 pp., Cont.-in-part of U.S. Ser. No. 703,484.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-4745
ICS A61K009-127; A61K009-20; A61K009-14
NCL 424465000; 424486000; 514283000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003059465	A1	20030327	US 2002-165867	20020606
	US 2002039594	A1	20020404	US 1998-75477	19980511
	WO 2003103596	A2	20031218	WO 2003-US17959	20030605
	WO 2003103596	A3	20040212		
	WO 2003103596	C1	20040422		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004009229	A1	20040115	US 2003-457068	20030605
	US 2004091541	A1	20040513	US 2003-622027	20030716
PRAI	US 1998-75477	A2	19980511		
	US 2000-478124	A2	20000105		

US 2000-703484	A2	20001031
US 1997-46379P	P	19970513
US 2001-828762	B1	20010409
US 2001-912609	A2	20010725
US 2002-165867	A2	20020606

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2003059465	ICM	A61K031-4745
	ICS	A61K009-127; A61K009-20; A61K009-14
	NCL	424465000; 424486000; 514283000
US 2003059465	ECLA	A61K009/107D; A61K009/51; A61K047/48W18B; A61K047/48W18; A61L029/16; A61L031/16
US 2004091541	ECLA	A61K009/51; A61K041/00M; A61K047/48W8D; A61K047/48W18B

OS MARPAT 138:260458

AB Pharmaceutical formulations are provided that increase the systemic bioavailability of Camptotheca compds., preferably, a **camptothecin** derivative, 7-ethyl-10-**hydroxycamptothecin** (SN-38). The drug is complexed with a stabilizing agent, but is not covalently bound thereto. Anionic or neutral lipids and/or polymers are used as stabilizing agents, and secondary stabilizing agents and/or other excipients may be incorporated into the formulation as well. Therapeutic methods are also provided, wherein a formulation of the invention is administered to a patient to treat a condition, disorder, or disease that is responsive to **camptothecin** derivs. Generally, administration is oral or parenteral. Twenty-five milliliters of SN-38 formulation were prepared containing SN-38-DOPG-poloxamine (2:8:1). This formulation was rehydrated with 25 mL unbuffered poloxamine solution and allowed to sit for 30-60 min. A microfluidizer was rinsed with the rehydration solution to fill 5 mL of microfluidizer dead volume and to achieve 30 mL final formulation rehydration volume The solution was microfluidized for 20 min. The resulting suspension was faintly yellow and translucent with some birefringence. Some settling of particulate matter occurred after 72 h refrigeration.

ST stabilized nanoparticle formulation Camptotheca

IT Intestine, neoplasm
(colon, adenocarcinoma; stabilized nanoparticle formulations of Camptotheca compds.)

IT Polyesters, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dilactone-based; stabilized nanoparticle formulations of Camptotheca compds.)

IT Drug delivery systems
(injections, i.v.; stabilized nanoparticle formulations of Camptotheca compds.)

IT Polyesters, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lactide; stabilized nanoparticle formulations of Camptotheca compds.)

IT Drug delivery systems
(nanoparticles; stabilized nanoparticle formulations of Camptotheca compds.)

IT Drug delivery systems
(oral; stabilized nanoparticle formulations of Camptotheca compds.)

IT Drug delivery systems
(parenterals; stabilized nanoparticle formulations of Camptotheca compds.)

IT Diglycerides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphorylated; stabilized nanoparticle formulations of Camptotheca compds.)

IT Drying
(spray; stabilized nanoparticle formulations of Camptotheca compds.)

IT Antitumor agents
Buffers

Camptotheca
Freeze drying
Particle size distribution
Stabilizing agents
(stabilized nanoparticle formulations of Camptotheca compds.)

IT Carbohydrates, biological studies
Lipids, biological studies
Phosphatidic acids
Phosphatidylcholines, biological studies
Phosphatidylethanolamines, biological studies
Phosphatidylinositols
Phosphatidylserines
Phospholipids, biological studies
Polymers, biological studies
Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilized nanoparticle formulations of Camptotheca compds.)

IT Drug delivery systems
(suspensions; stabilized nanoparticle formulations of Camptotheca compds.)

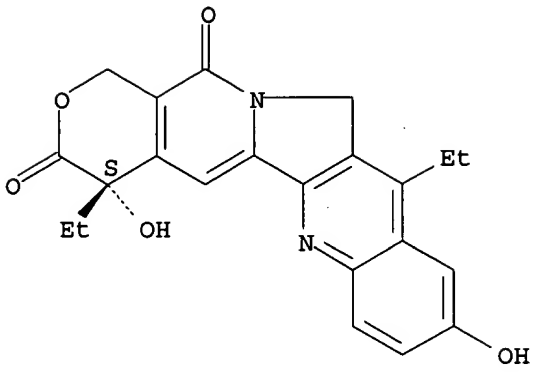
IT **86639-52-3**, SN-38
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilized nanoparticle formulations of Camptotheca compds.)

IT 56-81-5, Glycerol, biological studies 57-55-6, Propylene glycol, biological studies 64-17-5, Ethyl alcohol, biological studies 2644-64-6, Dipalmitoylphosphatidylcholine 4539-70-2, Distearoylphosphatidylcholine 5681-36-7, Dipalmitoylphosphatidylethanolamine 9003-11-6 9003-39-8, Polyvinyl pyrrolidone 10015-88-0, 1-Palmitoyl-2-oleoylphosphatidylethanolamine 18656-38-7, Dimyristoylphosphatidylcholine 18656-40-1, Dilauroylphosphatidylcholine **25322-68-3**, **Polyethylene glycol** 25322-69-4, Polypropylene oxide 26009-03-0, Polyglycolide 26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] 26202-08-4, Polyglycolide 26662-91-9, Palmitoyloleoylphosphatidylcholine 26680-10-4, Polylactide 26780-50-7, Poly(lactide-co-glycolide) 31694-55-0, **Polyethylene glycol** glyceryl ether 62700-69-0, Dioleoylphosphatidylglycerol 68737-67-7, Dioleoylphosphatidylcholine 81490-05-3, Palmitoyloleoylphosphatidylglycerol 106392-12-5, Poloxamer 110617-70-4, Tetronic 908 121366-88-9 502849-54-9
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilized nanoparticle formulations of Camptotheca compds.)

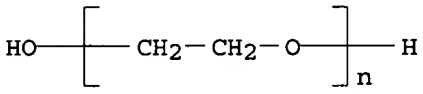
IT **86639-52-3**, SN-38
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilized nanoparticle formulations of Camptotheca compds.)

RN 86639-52-3 HCAPLUS
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 4,11-diethyl-4,9-dihydroxy-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT **25322-68-3, Polyethylene glycol**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilized nanoparticle formulations of Camptotheca compds.)
RN 25322-68-3 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



L99 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **2002:276433** HCAPLUS
DN **136:299693**
ED Entered STN: 12 Apr 2002
TI Novel targeted delivery systems for bioactive agents
IN **Unger, Evan C.; Matsunaga, Terry Onichi; Ramaswami, Varadarajan; Romanowski, Marek J.**
PA USA
SO U.S. Pat. Appl. Publ., 46 pp., Cont.-in-part of U.S. Ser. No. 703,474.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K009-14
ICS A61K039-395
NCL 424486000
CC 63-5 (Pharmaceuticals)
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002041898	A1	20020411	US 2001-912609	20010725
	US 6391687	B1	20020521	US 2000-703474	20001031
	WO 2003009881	A2	20030206	WO 2002-US22753	20020718
	WO 2003009881	A3	20040408		

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

	US 2004009229	A1	20040115	US 2003-457068	20030605
PRAI	US 2000-478124	A2	20000105		
	US 2000-703474	A2	20001031		
	US 2000-703484	A2	20001031		
	US 2001-912609	A	20010725		
	US 2002-165867	A2	20020606		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2002041898	ICM	A61K009-14
	ICS	A61K039-395
	NCL	424486000

AB Novel targeted delivery systems for bioactive agents are disclosed. In preferred form, the delivery systems comprise, in combination with an effective amount of a bioactive agent, a targeted matrix comprising a polymer and a targeting ligand. Preferably, the targeting ligand is covalently associated with the polymer and the bioactive agent is associated non-covalently with the polymer. Also in preferred embodiments, the bioactive agent is substantially homogeneously dispersed throughout the matrix. The compns. are particularly suitable as delivery vehicles with bioactive agents that have limited water solubility

ST targeted drug delivery system polymer matrix

IT Antibodies and Immunoglobulins
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bactericidins; targeted delivery systems for bioactive agents)

IT Polymers, biological studies
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(branched; targeted delivery systems for bioactive agents)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cells expressing; targeted delivery systems for bioactive agents)

IT Polymers, biological studies
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(co-; targeted delivery systems for bioactive agents)

IT Proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugates; targeted delivery systems for bioactive agents)

IT Peptides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclic; targeted delivery systems for bioactive agents)

IT Insecta
Scorpion
(defensins of; targeted delivery systems for bioactive agents)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(extracellular matrix-associated; targeted delivery systems for bioactive agents)

IT Cytokines
Gene
Glycopeptides
Glycoproteins
Hormones, animal, biological studies
Ligands
Peptides, biological studies
Polysaccharides, biological studies
Steroids, biological studies
Vitamins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(for drug targeting; targeted delivery systems for bioactive agents)

IT Polyesters, biological studies

RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lactide; targeted delivery systems for bioactive agents)

IT Drug delivery systems
(matrixes; targeted delivery systems for bioactive agents)

IT Micelles
(pharmaceutical; targeted delivery systems for bioactive agents)

IT Polymers, biological studies
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(poly(alkylenesulfonylalkyleneimine); targeted delivery systems for bioactive agents)

IT Sialic acids
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(poly; targeted delivery systems for bioactive agents)

IT Polymers, biological studies
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyalkene sulfides; targeted delivery systems for bioactive agents)

IT Polymers, biological studies
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyalkylene amines; targeted delivery systems for bioactive agents)

IT Polymers, biological studies
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyalkylene oxides; targeted delivery systems for bioactive agents)

IT Polymers, biological studies
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyalkylene sulfonates; targeted delivery systems for bioactive agents)

IT Polymers, biological studies
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyalkylene sulfones; targeted delivery systems for bioactive agents)

IT Polymers, biological studies
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyalkyleneimines; targeted delivery systems for bioactive agents)

IT Adrenal gland
Brain
Intestine
Kidney
Lung
Pancreas
Platelet (blood)
Skin
Uterus
(receptors of; targeted delivery systems for bioactive agents)

IT Eye
(retina, receptors of; targeted delivery systems for bioactive agents)

IT Polymers, biological studies
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(star-branched; targeted delivery systems for bioactive agents)

IT Antitumor agents
Drug delivery systems
Solubility
(targeted delivery systems for bioactive agents)

IT Fibronectins
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(targeted delivery systems for bioactive agents)
IT Polymers, biological studies
Polyoxyalkylenes, biological studies
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted delivery systems for bioactive agents)
IT Bacteriocins
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted delivery systems for bioactive agents)
IT Toxins
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted delivery systems for bioactive agents)
IT Growth factors, animal
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted delivery systems for bioactive agents)
IT Protamines
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thionins; targeted delivery systems for bioactive agents)
IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tissue-specific; targeted delivery systems for bioactive agents)
IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α5β1; targeted delivery systems for bioactive agents)
IT **7689-03-4**, **Camptothecin** 33069-62-4D, Paclitaxel, conjugates 114977-28-5D, Docetaxel, conjugates
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(targeted delivery systems for bioactive agents)
IT 176254-11-8 176254-15-2 176254-17-4 176254-18-5 176254-20-9 243961-35-5 243961-36-6 243961-37-7 243961-38-8 243961-39-9 243961-40-2 243961-47-9 243961-48-0 243961-53-7 243961-75-3 408512-67-4 408512-68-5
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted delivery systems for bioactive agents)
IT 79-10-7D, Acrylic acid, hydroxyalkyl derivative, polymers 79-41-4D, Methacrylic acid, hydroxyalkyl derivative, polymers 9002-89-5, Polyvinyl alcohol 9002-98-6 9003-09-2, Polyvinylmethylether 9003-11-6 9003-39-8, Polyvinylpyrrolidone 9064-17-9, Polypropylene sulfide 9086-85-5, Polyhydroxypropyl methacrylate 24936-67-2, Polyethylene sulfide 24980-34-5, Polyethylene sulfide **24980-41-4**, **Polycaprolactone** 25037-42-7, Polypropylene imine 25037-97-2, Polypropylene sulfide **25248-42-4**, **Polycaprolactone** **25322-68-3**, **Polyethylene glycol** 25322-69-4, Polypropylene glycol 25805-17-8, Polyethyloxazoline 26022-14-0, Polyhydroxyethylacrylate 26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] 26085-02-9, Poly[nitrilo(dichlorophosphoranylidyne)] 26101-52-0 26375-28-0 26680-10-4, Polylactide 26780-50-7, Poly(lactide-co-glycolide) 31694-55-0, Ethoxylated Glycerol 34344-66-6, Polysorbic acid 52352-27-9, Polyhydroxybutyric acid 53694-15-8, Ethoxylated Sorbitol 57118-63-5, Poly(sulfonyl-1,2-ethanediyl) 58548-19-9 61931-73-5, Ethoxylated glucose 102190-94-3, Polyhydroxyvaleric acid 158606-68-9, Polyaspartamide 158820-10-1 206859-46-3 408512-66-3
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted delivery systems for bioactive agents)
IT 9087-70-1, BPTI 37231-28-0, Melittin 55068-79-6, Bombinin

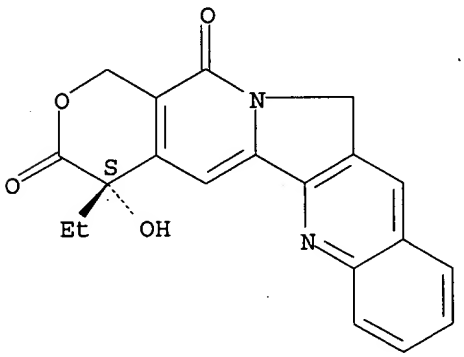
72093-21-1, Mastoparan 77752-27-3, Seminal plasmin 80802-79-5, Cecropin 95751-30-7, Charybdotoxin 97762-98-6, Brevinin 108334-53-8, Sarcotoxin 113041-69-3, Magainin 116229-36-8, Bactenecin 123997-21-7, Apidaecin 128906-89-8, Royalisin 131257-09-5, Bombolitin 131889-89-9, Esculentin 133425-01-1, Andropin 136212-91-4, Dermaseptin 138347-64-5 140896-21-5, Indolicidin 146897-68-9, Lactoferricin 148045-74-3, Polyphemusin 148045-87-8, Tachyplesin 149635-29-0 149635-35-8 **153477-08-8** 156476-39-0, β Defensin 159125-12-9 162227-40-9 163663-18-1, Protegrin 179048-25-0, Drosocin 179560-60-2 179560-62-4 179560-63-5 179560-64-6 179560-65-7 184654-51-1, Diptericin 189023-64-1 251460-81-8, α Defensin 408512-69-6 408512-70-9 408512-71-0 408512-72-1 408512-73-2 408512-74-3 408512-75-4 408512-76-5 408512-77-6 408512-78-7 408512-79-8 408512-80-1
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted delivery systems for bioactive agents)

IT 193562-90-2, Abaecin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted delivery systems for bioactive agents)

IT **7689-03-4, Camptothecin**
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(targeted delivery systems for bioactive agents)

RN 7689-03-4 HCAPLUS
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 4-ethyl-4-hydroxy-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

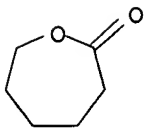


IT **24980-41-4, Polycaprolactone 25248-42-4, Polycaprolactone 25322-68-3, Polyethylene glycol**
RL: POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted delivery systems for bioactive agents)

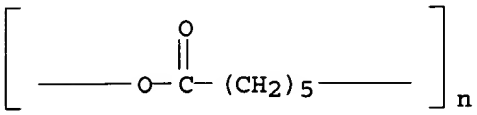
RN 24980-41-4 HCAPLUS
CN 2-Oxepanone, homopolymer (9CI) (CA INDEX NAME)

CM 1

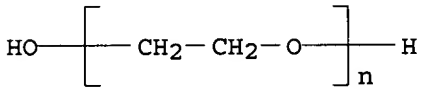
CRN 502-44-3
CMF C6 H10 O2



RN 25248-42-4 HCAPLUS
CN Poly[oxy(1-oxo-1,6-hexanediyl)] (9CI) (CA INDEX NAME)

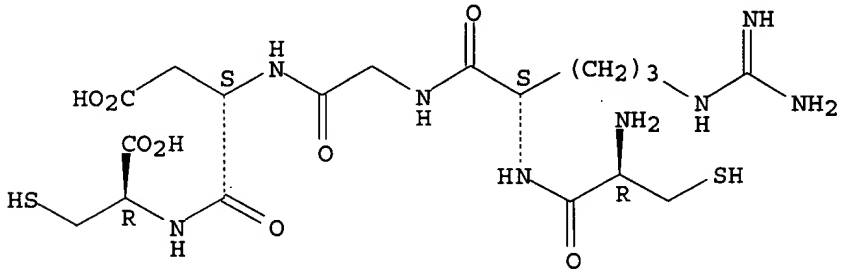


RN 25322-68-3 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



IT **153477-08-8**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeted delivery systems for bioactive agents)
RN 153477-08-8 HCAPLUS
CN L-Cysteine, L-cysteinyl-L-arginylglycyl-L-α-aspartyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L99 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:507513 HCAPLUS
DN 135:97475
ED Entered STN: 13 Jul 2001
TI Pharmaceutical formulations for the delivery of drugs having low aqueous solubility
IN **Unger, Evan C.; Romanowski, Marek J.**
PA **ImaRx Therapeutics, Inc., USA**
SO PCT Int. Appl., 80 pp.
CODEN: PIXXD2
DT Patent
LA English

IC ICM A61K009-14
ICS A61K009-127; A61K009-10; A61K009-19
CC 63-6 (Pharmaceuticals)
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001049268	A1	20010712	WO 2000-US35322	20001221
	W: AU, CA, JP				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
	EP 1246608	A1	20021009	EP 2000-988371	20001221
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
	JP 2003520210	T2	20030702	JP 2001-549636	20001221
PRAI	US 2000-478124	A	20000105		
	US 2000-703484	A	20001031		
	WO 2000-US35322	W	20001221		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001049268	ICM	A61K009-14
	ICS	A61K009-127; A61K009-10; A61K009-19

AB Pharmaceutical formulations are provided that increase the systemic bioavailability of a drug that has low aqueous solubility The drug is phys. entrapped by a spatially stabilized matrix of a hydrophilic polymer, but is not covalently bound thereto. Phospholipid moieties are optionally conjugated to the hydrophilic polymer, and free phospholipids, stabilizing agents and/or other excipients may be incorporated into the formulations as well. Therapeutic methods are also provided, wherein a formulation of the invention is administered to a patient to treat a condition, disorder or disease that is responsive to a particular drug. Generally, administration is oral or parenteral.

ST antitumor hydrophilic polymer matrix bioavailability; antibiotic hydrophilic polymer matrix bioavailability

IT Proteins, general, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blood; hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

IT Medical goods
(catheters, coating with paclitaxel/**PEG**; hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

IT Albumins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(denatured; hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

IT Agglutination
(factors for; hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

IT Lipoproteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(high-d.; hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

IT Antibiotics
Antitumor agents
Antiviral agents
Drug bioavailability
(hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

IT Enzymes, biological studies
Growth factors, animal
Hormones, animal, biological studies
Immunoglobulins

Phosphatidic acids
Phosphatidylcholines, biological studies
Phosphatidylethanolamines, biological studies
Phosphatidylinositols
Phosphatidylserines
Phospholipids, biological studies
Polyoxyalkylenes, biological studies
Steroids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

IT P-glycoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

IT Lipoproteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(low-d.; hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

IT Proteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nuclear-binding; hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

IT Drug delivery systems
(oral; hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

IT Drug delivery systems
(parenterals; hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

IT Diglycerides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphorylated; hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

IT Albumins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serum; hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

IT Medical goods
(stents, coating with paclitaxel/**PEG**; hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

IT Proteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structural; hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

IT Lipoproteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(very-low-d.; hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

IT 56-81-5, Glycerol, biological studies 64-17-5, Ethanol, biological studies 81-25-4, Cholic acid 145-42-6, Sodium taurocholate 302-95-4, Sodium deoxycholate 361-09-1, Sodium cholate 2836-32-0, Sodium glycolate 5681-36-7, Dipalmitoylphosphatidylethanolamine **7689-03-4**, **Camptothecin** 9002-01-1, Streptokinase 9002-89-5, Polyvinyl alcohol 9003-11-6, **Ethylene oxide** -propylene oxide copolymer 9003-39-8, PVP 9005-65-6, Tween 80 9039-53-6, Urokinase 9040-61-3, Staphylokinase 10015-88-0, 1-Palmitoyl-2-oleoylphosphatidylethanolamine **25322-68-3**, **Polyethylene glycol** 25322-69-4, Polypropylene oxide 26009-03-0, Polyglycolide 26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] 26202-08-4, Polyglycolide 26680-10-4, Polylactide 26780-50-7, Lactide-glycolide copolymer 33069-62-4, Paclitaxel 37221-79-7, Vasoactive intestinal peptide 59865-13-3, Cyclosporin A

74381-53-6, Leuprolide acetate 85637-73-6, Atrial natriuretic peptide
114977-28-5, Docetaxel 116243-73-3, Endothelin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD

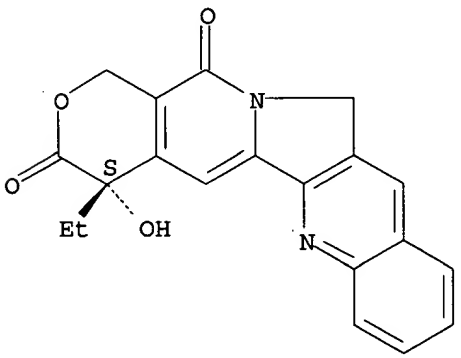
RE

(1) Axelsson; US 4693999 A 1987 HCAPLUS
(2) Desai; US 5916596 A 1999 HCAPLUS
(3) Desai; US 6096331 A 2000 HCAPLUS
(4) Durzan; US 5981777 A 1999 HCAPLUS
(5) Plate; US 6004583 A 1999 HCAPLUS
(6) Samyang Genex Co Ltd; Genexol, TM# 2,322,035 2000
(7) Wood; US 5288503 A 1994 HCAPLUS
(8) Woodle; US 5013556 A 1991 HCAPLUS

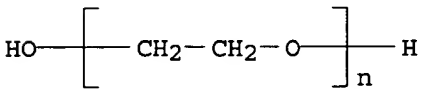
IT **7689-03-4, Camptothecin 25322-68-3, Polyethylene glycol**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydrophilic polymer matrix containing stabilizers for delivery of drugs having low aqueous solubility)

RN 7689-03-4 HCAPLUS
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 4-ethyl-4-hydroxy-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 25322-68-3 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



L99 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:766507 HCAPLUS
DN 130:29221
ED Entered STN: 08 Dec 1998
TI Preparation of solid porous matrixes for pharmaceutical uses
IN **Unger, Evan C.**
PA **ImaRx Pharmaceutical Corp., USA**
SO PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DT Patent
LA English

IC ICM A61K009-10
CC 63-6 (Pharmaceuticals)
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9851282	A1	19981119	WO 1998-US9570	19980512
	W: AU, BR, CA, CN, JP, KR, NZ				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 2002039594	A1	20020404	US 1998-75477	19980511
	AU 9873787	A1	19981208	AU 1998-73787	19980512
	EP 983060	A1	20000308	EP 1998-921109	19980512 <--
	R: DE, FR, GB, IT, NL				
	US 2001018072	A1	20010830	US 2001-828762	20010409
	US 2004091541	A1	20040513	US 2003-622027	20030716
PRAI	US 1997-46379P	P	19970513		
	US 1998-75477	A	19980511		
	WO 1998-US9570	W	19980512		
	US 2001-828762	B1	20010409		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9851282	ICM	A61K009-10
WO 9851282	ECLA	A61K009/51; A61K041/00M; A61K047/48W8D; A61K047/48W18B
US 2004091541	ECLA	A61K009/51; A61K041/00M; A61K047/48W8D; A61K047/48W18B

AB A solid porous matrix formed from a surfactant, a solvent, and a bioactive agent is described. Thus, amphotericin nanoparticles were prepared by using ZrO2 beads and a surfactant. The mixture was milled for 24 h.

ST solid porous matrix pharmaceutical surfactant
IT Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(A; preparation of solid porous matrixes for pharmaceutical uses)
IT Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(G; preparation of solid porous matrixes for pharmaceutical uses)
IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GPIIBIIIa; preparation of solid porous matrixes for pharmaceutical uses)
IT Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(M; preparation of solid porous matrixes for pharmaceutical uses)
IT Macrophage
(activation factor; preparation of solid porous matrixes for pharmaceutical uses)
IT Steroids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(acyl; preparation of solid porous matrixes for pharmaceutical uses)
IT Quaternary ammonium compounds, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alkylbenzyldimethyl, chlorides; preparation of solid porous matrixes for pharmaceutical uses)
IT Estrogens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiestrogens; preparation of solid porous matrixes for pharmaceutical uses)
IT Ethers, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclic; preparation of solid porous matrixes for pharmaceutical uses)
IT Eye, disease
(diabetic retinopathy; preparation of solid porous matrixes for pharmaceutical uses)
IT Ethers, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(diethers; preparation of solid porous matrixes for pharmaceutical uses)
IT Natural products, pharmaceutical
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(digitalis; preparation of solid porous matrixes for pharmaceutical uses)
IT Polyesters, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dilactone-based; preparation of solid porous matrixes for pharmaceutical uses)
IT Toxins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endotoxins; preparation of solid porous matrixes for pharmaceutical uses)
IT **Polyoxyalkylenes**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ethers; preparation of solid porous matrixes for pharmaceutical uses)
IT Polyesters, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lactic acid-based; preparation of solid porous matrixes for pharmaceutical uses)
IT Ethers, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methoxyl; preparation of solid porous matrixes for pharmaceutical uses)
IT Drug delivery systems
(microparticles; preparation of solid porous matrixes for pharmaceutical uses)
IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal; preparation of solid porous matrixes for pharmaceutical uses)
IT Drug delivery systems
(nanoparticles; preparation of solid porous matrixes for pharmaceutical uses)
IT Surfactants
(nonionic; preparation of solid porous matrixes for pharmaceutical uses)
IT Natural products, pharmaceutical
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opium; preparation of solid porous matrixes for pharmaceutical uses)
IT Polyethers, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ortho ester group-containing; preparation of solid porous matrixes for pharmaceutical uses)
IT Perfluoro compounds
Perfluoro compounds
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(perfluoroalkyl ethers; preparation of solid porous matrixes for pharmaceutical uses)
IT Ethers, biological studies
Ethers, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(perfluoroalkyl; preparation of solid porous matrixes for pharmaceutical uses)
IT Allergy inhibitors
Anesthetics
Anti-inflammatory agents
Antianginal agents
Antibiotics
Anticoagulants
Antirheumatic agents
Antitumor agents
Antiviral agents
Blood products
Coryneform bacteria
Drug delivery systems
Fungicides
Hypnotics and Sedatives

Mycobacterium
Narcotics
Neuromuscular blocking agents
Preservatives
Protozoacides
Tuberculostatics
(preparation of solid porous matrixes for pharmaceutical uses)

IT Ligands
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Albumins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Canola oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Carbohydrates, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Collagens, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Corn oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Crown ethers
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Elastins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Enkephalins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Enzymes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Fibrins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Glycosides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Hormones, animal, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Integrins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Interleukin 1
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Interleukin 10
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Interleukin 11
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT Interleukin 12
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of solid porous matrixes for pharmaceutical uses)
IT Interleukin 2
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
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(preparation of solid porous matrixes for pharmaceutical uses)
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IT Interleukin 6
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(preparation of solid porous matrixes for pharmaceutical uses)
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(preparation of solid porous matrixes for pharmaceutical uses)
IT Interleukin 9
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Interleukins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Lipids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Lipopolysaccharides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Lymphokines
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Lymphotoxin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Olive oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Peanut oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Peptides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Perfluorocarbons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Platelet-derived growth factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Polyethers, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Polymers, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT **Polyoxyalkylenes**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of solid porous matrixes for pharmaceutical uses)
IT Polyphosphazenes
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Polysaccharides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Porphyrins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Prostaglandins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Proteins, general, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Retinoids
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Ricins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Safflower oil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Terpenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Transforming growth factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Tumor necrosis factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Vitamins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α-2a; preparation of solid porous matrixes for pharmaceutical uses)
IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α-2b; preparation of solid porous matrixes for pharmaceutical uses)
IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α; preparation of solid porous matrixes for pharmaceutical uses)
IT Lactams
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β-, antibiotics; preparation of solid porous matrixes for pharmaceutical uses)
IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β; preparation of solid porous matrixes for pharmaceutical uses)
IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(γ; preparation of solid porous matrixes for pharmaceutical uses)
IT 101479-70-3, Adaprolol
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Adaprolol; preparation of solid porous matrixes for pharmaceutical uses)
IT 64228-81-5, Atracurium besilate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Atracurium besilate; preparation of solid porous matrixes for pharmaceutical uses)

IT 50-07-7, Mitomycin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Mitomycin; preparation of solid porous matrixes for pharmaceutical uses)
IT 9015-82-1 9028-31-3, Aldose reductase 125978-95-2, Nitric oxide synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; preparation of solid porous matrixes for pharmaceutical uses)
IT 9081-34-9, 5α-Reductase
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors; preparation of solid porous matrixes for pharmaceutical uses)
IT 9031-44-1, Kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ligands for metalloprotein; preparation of solid porous matrixes for pharmaceutical uses)
IT 9054-89-1, Superoxide dismutase
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(manganese-dependent; preparation of solid porous matrixes for pharmaceutical uses)
IT 9001-12-1, Collagenase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of solid porous matrixes for pharmaceutical uses)
IT 591-93-5P, 1,4-Pentadiene 216245-34-0P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
IT 50-02-2, Dexamethasone 50-03-3, Hydrocortisone acetate 50-04-4, Cortisone acetate 50-23-7 50-24-8, Prednisolone 50-28-2, Estra-1,3,5(10)-triene-3,17-diol (17β)-, biological studies 50-33-9, Phenylbutazone, biological studies 50-44-2, Mercaptopurine 50-67-9, 5-Hydroxytryptamine, biological studies 50-76-0, Dactinomycin 50-78-2, Aspirin 50-99-7, D-Glucose, biological studies 51-05-8, Procaine hydrochloride 51-61-6, Dopamine, biological studies 52-21-1, Prednisolone acetate 52-53-9, Verapamil 52-67-5, Penicillamine 52-86-8, Haloperidol 53-02-1 53-03-2, Prednisone 53-19-0, Mitotane 53-36-1, Methylprednisolone acetate 53-41-8D, Androsterone, aza derivs. 53-86-1, Indomethacin 54-05-7, Chloroquine 54-85-3, Isoniazid 55-63-0, Nitroglycerin 55-98-1, Busulfan 56-75-7, Chloramphenicol 56-81-5, 1,2,3-Propanetriol, biological studies 57-09-0, Cetyltrimethylammonium bromide 57-22-7, Vincristine 57-27-2, Morphine, biological studies 57-30-7, Phenobarbital sodium 57-33-0, Pentobarbital sodium 57-43-2, Amobarbital 57-48-7, Fructose, biological studies 57-50-1, Sucrose, biological studies 57-55-6, 1,2-Propanediol, biological studies 57-83-0, Progesterone, biological studies 57-94-3, Tubocurarine chloride 58-22-0, Testosterone 58-32-2, Dipyridamole 58-82-2, Bradykinin 59-02-9, α-Tocopherol 59-05-2, Methotrexate 59-23-4, Galactose, biological studies 59-30-3, Folic acid, biological studies 60-54-8, Tetracycline 61-32-5, Methicillin 61-33-6, biological studies 61-68-7, Mefenamic acid 64-43-7, Amobarbital sodium 65-29-2, Gallamine triethiodide 65-49-6, Para-aminosalicylic acid 66-79-5, Oxacillin 67-56-1, Methanol, biological studies 67-78-7, Triamcinolone diacetate 67-97-0, Cholecalciferol 68-41-7, Cycloserine 69-53-4, Ampicillin 69-72-7D, Salicylic acid, esters 70-18-8, Glutathione, biological studies 71-27-2, Succinylcholine chloride 71-63-6, Digitoxin 71-73-8, Thiopental sodium 73-78-9, Lidocaine hydrochloride 74-82-8, Methane, biological studies 74-99-7, Propyne 75-00-3, Chloroethane 75-10-5, Difluoromethane 75-18-3, Methyl sulfide 75-19-4, Cyclopropane 75-29-6, Propane-2-chloro 75-31-0, 2-AminoPropane, biological studies 75-34-3, 1,1-Dichloroethane 75-35-4, 1,1-Dichloroethylene, biological studies 75-43-4, Dichlorofluoromethane 75-45-6, Chlorodifluoromethane 75-46-7, TriFluoromethane 75-56-9, biological studies 75-61-6, Dibromodifluoromethane 75-63-8, Bromotrifluoromethane 75-69-4, Trichlorofluoromethane 75-71-8, Dichlorodifluoromethane 75-72-9,

Chlorotrifluoromethane 75-73-0 76-13-1, 1,1,2-Trichloro-1,2,2-Trifluoroethane 76-15-3, 1-Chloro-1,1,2,2,2-Pentafluoroethane 76-16-4, HexaFluoroethane 76-19-7, Octafluoropropane 76-25-5, Triamcinolone acetonide 76-57-3, Codeine 76-74-4, Pentobarbital 76-99-3, Methadone 77-02-1, Aprobarbital 77-21-4, Glutethimide 78-11-5, Pentaerythritol tetranitrate 78-78-4, 2-Methylbutane 78-79-5, 2-Methyl-1,3-Butadiene, biological studies 78-80-8, 2-Methyl-1-Buten-3-yne 79-10-7D, Acrylic acid, esters, polymers 79-17-4, Hydrazinecarboximidamide 80-08-0, Dapsone 83-43-2, Methylprednisolone 87-33-2, Isosorbide dinitrate 92-13-7, Pilocarpine 95-80-7, 2,4-Diaminotoluene 96-40-2, 3-Chloro-cyclopentene 96-49-1, 1,3-Dioxolan-2-one 98-96-4, Pyrazinamide 99-20-7, Trehalose 103-90-2, Acetaminophen 106-98-9, 1-Butene, biological studies 106-99-0, 1,3-Butadiene, biological studies 107-00-6, 1-Butyne 107-01-7, 2-Butene 107-25-5, Methyl vinyl ether 109-66-0, n-Pentane, biological studies 109-67-1, 1-Pentene 109-92-2 109-93-3, Vinyl ether 111-02-4, Squalene 113-18-8, Ethchlorvynol 114-07-8, Erythromycin 115-07-1, 1-Propene, biological studies 115-10-6, Methyl ether 115-25-3, OctafluoroCyclobutane 115-44-6, Talbutal 116-15-4, Hexafluoropropylene 118-42-3, Hydroxychloroquine 122-18-9, Benzyldimethylhexadecylammonium chloride 122-57-6 123-03-5, Cetylpyridinium chloride 123-63-7, Paraldehyde 124-03-8, Cetyldimethylethylammonium bromide 124-40-3, Dimethylamine, biological studies 124-94-7, Triamcinolone 125-02-0, Prednisolone sodium phosphate 125-04-2, Hydrocortisone sodium succinate 125-64-4, Methyprylon 125-84-8, Aminoglutethimide 126-07-8, Griseofulvin 126-52-3, Ethinamate 129-20-4, Oxyphenbutazone 130-15-4, 1,4-Naphthalenedione 130-95-0, Quinine 133-51-7, Meglumine antimonate 135-16-0 136-47-0, Tetracaine hydrochloride 139-07-1, Benzyldimethyldodecylammonium chloride 139-08-2, Benzyldimethyltetradecylammonium chloride 140-72-7, Cetylpyridinium bromide 143-67-9, Vinblastine sulfate 143-81-7, Butabarbital sodium 147-52-4, Nafcillin 147-94-4, Cytosine arabinoside 148-82-3, Melphalan 151-73-5, Betamethasone sodium phosphate 154-21-2, Lincomycin 287-23-0, Cyclobutane 302-17-0, Chloral hydrate 305-03-3 307-34-6, Perfluorooctane 307-45-9, Perfluorodecane 309-36-4, Methohexital sodium 309-43-3, Secobarbital sodium 317-52-2, Hexafluorenium bromide 334-99-6, NitrosotriFluoromethane 335-02-4, NitrotriFluoromethane 335-05-7, Trifluoromethanesulfonyl fluoride 335-57-9, Perfluoroheptane 338-65-8, 2-Chloro-1,1-Difluoroethane 350-51-6, 3-Fluorostyrene 353-36-6, Fluoroethane 353-85-5, Trifluoroacetonitrile 353-87-7, BromodifluoronitrosoMethane 354-72-3, Nitrosopentafluoroethane 354-80-3, Perfluoroethylamine 354-81-4, Nitropentafluoroethane 355-25-9, Decafluorobutane 355-42-0, Perfluorohexane 355-79-3, Perfluorotetrahydropyran 357-26-6, Perfluoro-1-Butene 359-35-3, 1,1,2,2-Tetrafluoroethane 360-89-4, Octafluoro-2-butene 366-70-1, Procarbazine-hydrochloride 371-67-5, 1,1,1-Trifluoro-diazoethane 371-77-7 371-78-8, Trifluoromethyl sulfide 373-52-4, Bromofluoromethane 374-07-2, 1,1-Dichloro-1,2,2,2-Tetrafluoroethane 375-96-2, Perfluorononane 376-87-4, Perfluoro-1-pentene 378-44-9, Betamethasone 420-45-1, Propane-2,2-difluoro 420-46-2, 1,1,1-Trifluoroethane 421-17-0, Trifluoromethanesulfenylchloride 421-83-0, Trifluoromethanesulfonyl chloride 423-26-7 423-33-6 435-97-2, Phenprocoumon 443-48-1, Metronidazole 460-12-8, Diacetylene 461-68-7, TetrafluoroAllene 463-49-0, Allene 463-58-1, Carbonyl sulfide 463-82-1, Neopentane 503-17-3, 2-Butyne 508-99-6, Hydrocortisone cypionate 514-36-3, Fludrocortisone acetate 525-66-6 536-33-4, Ethionamide 547-64-8, Methyl lactate 548-73-2, Droperidol 557-98-2, 2-Chloropropylene 559-40-0, Octafluorocyclopentene 561-27-3, Heroin 563-45-1, 3-Methyl-1-Butene 563-46-2, 2-Methyl-1-Butene 582-24-1D, Benzoylcarbinol, salts 590-19-2, 1,2-Butadiene 590-21-6, 1-ChloroPropylene 593-53-3, Fluoromethane 593-70-4, Chlorofluoromethane 593-98-6, Bromochlorofluoromethane 594-11-6, MEthylCyclopropane 595-33-5, Megestrol acetate 598-23-2,

3-Methyl-1-Butyne 598-53-8, Methyl isopropyl ether 598-56-1
598-61-8, MethylCyclobutane 624-72-6, 1,2-Difluoroethane 624-91-9,
Methyl nitrite 625-04-7, 2-Pentanone-4-amino-4-methyl 627-20-3,
cis-2-Pentene 632-58-6, Phthalic acid-tetrachloro 644-62-2
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT 646-04-8, trans-2-Pentene 661-54-1, Propyne-3,3,3-trifluoro 661-97-2
677-56-5, Propane-1,1,1,2,2,3-hexafluoro 678-26-2, Perfluoropentane
684-16-2, Hexafluoroacetone 685-63-2, Hexafluoro-1,3-butadiene
689-97-4, Vinyl acetylene 692-50-2, Hexafluoro-2-butyne 752-61-4,
Digitalin 768-94-5, Amantadine 818-92-8, 3-FluoroPropylene 846-50-4,
Temazepam 921-13-1, Chlorodinitromethane 927-84-4, Trifluoromethyl
peroxide 928-45-0, Butyl nitrate 968-93-4, Testolactone 987-24-6,
Betamethasone acetate 990-73-8, Fentanyl citrate 1070-11-7, Ethambutol
hydrochloride 1119-94-4, Lauryltrimethylammonium bromide 1119-97-7,
Myristyltrimethylammonium bromide 1172-18-5 1177-87-3, Dexamethasone
acetate 1191-96-4, EthylCyclopropane 1306-06-5, Hydroxylapatite
1397-89-3, Amphotericin B 1400-61-9, Nystatin 1404-04-2, Neomycin
1405-37-4, Capreomycin sulfate 1493-03-4, Difluoroiodomethane
1597-82-6, Paramethasone acetate 1630-94-0, 1,1-DimethylCyclopropane
1691-13-0, 1,2-Difluoroethylene 1722-62-9, Mepivacaine hydrochloride
1759-88-2 1867-66-9, Ketamine hydrochloride 2022-85-7, Flucytosine
2068-78-2, Vincristine sulfate 2314-97-8, IodotriFluoromethane
2366-52-1, 1-Fluorobutane 2375-03-3, Methylprednisolone sodium succinate
2392-39-4, Dexamethasone sodium phosphate 2511-95-7,
1,2-DimethylCyclopropane 2551-62-4, Sulfur hexafluoride 3116-76-5,
Dicloxacillin 3385-03-3, Flunisolide 3458-28-4, Mannose 3485-14-1,
Cyclacillin 3511-16-8, Hetacillin 3529-04-2,
Benzyldimethylhexadecylammonium bromide 3810-74-0, Streptomycin sulfate
3858-89-7, Chloroprocaine hydrochloride 4185-80-2, Methotrimeprazine
hydrochloride 4428-95-9, Foscarnet 4431-00-9, Aurintricarboxylic acid
4697-36-3, Carbenicillin 4786-20-3, Crotononitrile 4901-75-1,
3-Ethyl-3-methyldiaziridine 5534-09-8, Beclomethasone dipropionate
5536-17-4, Arabinosyl adenine 5611-51-8, Triamcinolone hexacetonide
5714-22-7, Sulfur fluoride (S2F10) 6000-74-4, Hydrocortisone sodium
phosphate 7281-04-1, Benzyldimethyldodecylammonium bromide 7297-25-8,
Erythritol tetranitrate 7439-89-6, Iron, biological studies 7440-01-9,
Neon, biological studies 7440-06-4D, Platinum, compds., biological
studies 7440-15-5, Rhenium, biological studies 7440-24-6, Strontium,
biological studies 7440-26-8, Technetium, biological studies
7440-48-4, Cobalt, biological studies 7440-63-3, Xenon, biological
studies 7440-65-5, Yttrium, biological studies 7601-55-0, Metocurine
iodide 7637-07-2, biological studies 7647-14-5, Sodium chloride,
biological studies 7681-14-3, Prednisolone tebutate 7727-37-9,
Nitrogen, biological studies 7728-73-6 7782-41-4, Fluorine, biological
studies 7782-44-7, Oxygen, biological studies 7783-82-6, Tungsten
hexafluoride 9001-75-6, Pepsin 9001-78-9, Alkaline phosphatase
9002-01-1, Streptokinase 9002-04-4, Thrombin 9002-60-2,
Adrenocorticotropic hormone, biological studies 9002-61-3 9002-72-6,
Growth hormone 9002-79-3, Melanocyte stimulating hormone 9002-89-5,
Poly(vinyl alcohol) 9003-11-6 9003-39-8, PVP 9004-10-8, Insulin,
biological studies 9004-34-6, Cellulose, biological studies 9004-54-0,
Dextran, biological studies 9004-61-9, Hyaluronic acid 9004-67-5,
Methyl Cellulose 9005-25-8, Starch, biological studies 9005-27-0,
HETA-starch 9005-32-7, Alginic acid 9005-49-6, Heparin, biological
studies 9005-64-5, **Polyoxyethylene** sorbitan monolaurate
9005-65-6, **Polyoxyethylene** sorbitan monooleate 9005-66-7,
Polyoxyethylene sorbitan monopalmitate 9005-67-8,
Polyoxyethylene sorbitan monostearate 9005-71-4,
Polyoxyethylene sorbitan tristearate 9007-12-9, Calcitonin
9007-92-5, Glucagon, biological studies 9011-14-7, PMMA 9011-97-6,
Cholecystokinin 9015-68-3, Asparaginase 9015-71-8, Corticotropin
releasing factor 9036-19-5, Octoxynol 9039-53-6, Urokinase

9061-61-4, Nerve growth factor 10024-97-2, Nitrogen oxide (N2O), biological studies 11000-17-2, Vasopressin 11056-06-7, Bleomycin 11096-26-7, Erythropoietin 13264-41-0, Cetyldimethylethylammonium chloride 13292-46-1, Rifampin 13311-84-7, Flutamide 13647-35-3, Trilostane 15500-66-0, Pancuronium bromide 15663-27-1, Cisplatin 15686-71-2, Cephalexin 15687-27-1, Ibuprofen 16009-13-5, Hemin 16136-85-9 17598-65-1, Deslanoside 18010-40-7, Bupivacaine hydrochloride 18323-44-9, Clindamycin 18378-89-7, Plicamycin 18773-88-1, Benzyldimethyltetradecylammonium bromide 20187-55-7, Bendazac 20274-91-3 20830-75-5, Digoxin 21829-25-4, Nifedipine 22204-53-1, Naproxen 22494-42-4, Diflunisal 22916-47-8, Miconazole 23110-15-8, Fumagillin 23541-50-6, Daunorubicin hydrochloride 24356-66-9 24764-97-4, 2-Bromobutyraldehyde 24991-23-9 25104-18-1, Polylysine 25151-81-9, Prostanoic acid 25316-40-9, Adriamycin **25322-68-3 25322-68-3D, PEG**, ethers 25322-69-4, Polypropylene glycol 25513-46-6, Polyglutamic acid 26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] 26100-51-6, Poly(lactic acid) 26171-23-3, Tolmetin 26780-50-7, Glycolide-lactide copolymer 26787-78-0, Amoxicillin 26839-75-8, Timolol 28911-01-5, Triazolam 29121-60-6, Vaninolol 29767-20-2, Teniposide 30516-87-1, Azidothymidine 31637-97-5, Etofibrate 33069-62-4, Taxol 33125-97-2, Etomidate 33419-42-0, Etoposide 33507-63-0, Substance p 34077-87-7, DiChlorotrifluoroethane 34787-01-4, Ticarcillin 36322-90-4 36637-19-1, Etidocaine hydrochloride 36791-04-5, Ribavirin 38000-06-5, Polylysine 38194-50-2, Sulindac 38821-53-3, Cephradine 39391-18-9, Cyclooxygenase 41575-94-4, Carboplatin 42399-41-7, Diltiazem 47141-42-4, Levobunolol 50370-12-2, Cefadroxil 50402-72-7, Piperidine-2,3,6-trimethyl 50700-72-6, Vecuronium bromide 50972-17-3, Bacampicillin 51264-14-3, Amsacrine 52205-73-9, Estramustine phosphate sodium 52365-63-6, Dipivefrin 53045-71-9, 1-Pentene-3-bromo 53188-07-1, Trolox 53678-77-6, Muramyldipeptide 53994-73-3, Cefaclor 54965-24-1, Tamoxifen citrate 55142-85-3, Ticlopidine 57223-18-4, 1-Nonen-3-yne 59277-89-3, Acyclovir 59467-96-8, Midazolam hydrochloride 60118-07-2, Endorphin 62031-54-3, Fibroblast growth factor 62229-50-9, Epidermal growth factor 62232-46-6, Bifemelane hydrochloride 62571-86-2, Captopril 62683-29-8, Colony stimulating factor 63659-18-7, Betaxolol 65277-42-1, Ketoconazole 68302-57-8 68367-52-2, Sorbinil 69279-90-9, Ansamitocin 72702-95-5, Ponalrestat 73218-79-8, Apraclonidine hydrochloride 73984-11-9 74381-53-6, Leuprolide acetate 74790-08-2, Spiroplatin 75847-73-3, Enalapril 76547-98-3, Lisinopril 77181-69-2, Sorivudine 80755-87-9 81486-22-8, Nipradilol 82159-09-9, Epalrestat 82410-32-0, Ganciclovir 82964-04-3, Tolrestat 83869-56-1, Granulocyte macrophage colony stimulating factor 86090-08-6, Angiostatin 88096-12-2 89149-10-0, 15-Deoxyspergualin 98023-09-7 99896-85-2 106956-32-5, Oncostatin M 113852-37-2, Cidofovir 116632-15-6, 1.2.3-Nonadecanetricarboxylic acid 2-hydroxytrimethylester 119813-10-4, Carzelesin 120279-96-1, Dorzolamide 120287-85-6D, Cetrorelix, derivs. 121181-53-1, Filgrastim 124389-07-7, Muramyltripeptide 127464-60-2, Vascular endothelial growth factor
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT 127984-74-1, Somatuline 130209-82-4, Latanoprost 139639-23-9, Tissue plasminogen activator 141436-78-4, Protein kinase c 143011-72-7, Granulocyte colony stimulating factor 148717-90-2, Squalamine 163702-07-6 169939-94-0, LY333531 216245-16-8 216245-28-2 216245-32-8 216382-88-6, Imidazopyridine 216441-58-6, Lecosim
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)

IT 9001-92-7, Protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(receptors; preparation of solid porous matrixes for pharmaceutical uses)

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE
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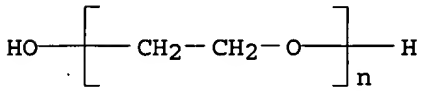
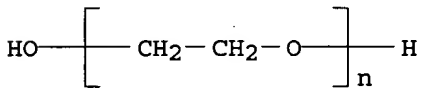
IT **25322-68-3 25322-68-3D, PEG**, ethers
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of solid porous matrixes for pharmaceutical uses)
RN 25322-68-3 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



RN 25322-68-3 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



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AN 2003:924309 HCAPLUS
DN 141:195078
ED Entered STN: 26 Nov 2003
TI Targeting of lipid-protamine-DNA (LPD) lipopolyplexes using RGD motifs
AU Harvie, Pierrot; Dutzar, Benjamin; Galbraith, Todd; Cudmore, Sally; O'Mahony, Daniel; Anklesaria, Pervin; Paul, Ralph
CS Targeted Genetics Corporation, Seattle, WA, USA
SO Journal of Liposome Research (2003), 13(3&4), 231-247
CODEN: JLREE7; ISSN: 0898-2104
PB Marcel Dekker, Inc.
DT Journal
LA English
CC 63-6 (Pharmaceuticals)
AB The incorporation of pegylated lipid into Lipid-Protamine-DNA (LPD-**PEG**) lipopolyplexes causes a decrease of their in vitro transfection activity. This can be partially attributed to a reduction in particle binding to cells. To restore particle binding and specifically target LPD formulations to tumor cells, the lipid-peptide conjugate DSPE-PEG5K-succinyl-**ACDCRGDCFCG**-COOH(DSPE-PEG5K-RGD-4C) was generated and incorporated into LPD formulations (LPD-**PEG**-RGD). LPD-**PEG**-RGD was characterized with respect to its biophys. and biol. properties. The Incorporation of DSPE-PEG5K-RGD-4C ligands into LPD formulations results in a 5 and a 15 fold increase in the LPD-**PEG** -RGD binding and uptake, resp., over an LPD-**PEG** formulation. Enhancement of binding and uptake resulted in a 100 fold enhancement of transfection activity. Moreover, this transfection enhancement was specific to cells expressing appropriate integrin receptors (MDA-MB-231). Huh7 cells, known for their low level of αvβ3 and αvβ5 integrin expression, failed to show RGD mediated transfection enhancement. This transfection enhancement can be abolished in a competitive manner using free RGD peptide, but not an RGE control peptide. Results demonstrated RGD mediated enhanced LPD-**PEG** cell binding and transfection in cells expressing the integrin receptor.

These formulations provide the basis for effective, targeted, systemic gene delivery.

ST lipid protamine DNA lipopolyplex targeting RGD peptide

IT Drug delivery systems
(liposomes; targeting of lipid-protamine-DNA (LPD) lipopolyplexes using RGD motifs)

IT Transformation, genetic
(targeting of lipid-protamine-DNA (LPD) lipopolyplexes using RGD motifs)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(targeting of lipid-protamine-DNA (LPD) lipopolyplexes using RGD motifs)

IT DNA
Protamines
RGD peptides
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting of lipid-protamine-DNA (LPD) lipopolyplexes using RGD motifs)

IT 144189-73-1, Dotap 182280-69-9 737764-90-8
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting of lipid-protamine-DNA (LPD) lipopolyplexes using RGD motifs)

IT 57-88-5, Cholesterol, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting of lipid-protamine-DNA (LPD) lipopolyplexes using RGD motifs)

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L100 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:845986 HCAPLUS
DN 139:73841
ED Entered STN: 07 Nov 2002
TI An angiogenic, endothelial-cell-targeted polymeric gene carrier
AU Suh, Wonhee; Han, Sang-Oh; Yu, Lei; Kim, Sung Wan
CS Department of Pharmaceutics and Pharmaceutical Chemistry, Center for Controlled Chemical Delivery, University of Utah, Salt Lake City, UT, 84112, USA
SO Molecular Therapy (2002), 6(5), 664-672
CODEN: MTOHCK; ISSN: 1525-0016
PB Elsevier Science
DT Journal
LA English
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 3
AB Targeting is one of the primary considerations in designing a specific and efficient gene delivery system. Here, an angiogenic endothelial cell-targeted polymeric gene delivery carrier was developed by conjugating an αvβ3/αvβ5 integrin-binding RGD peptide, **ACDCRGDCFC**, into the cationic polymer polyethyleneimine (PEI) via a hydrophilic **poly(ethylene glycol)** (**PEG**) spacer. The incorporation of **PEG** into PEI improved the poor physicochem. properties of PEI-DNA complexes. At a neutral charge ratio, DNA complexes with PEI were polydisperse and substantially aggregated, whereas DNA complexes with PEI-g-1PEG-RGD were homogeneous with 100-200 nm effective diameter Their surface charge was also significantly reduced due to the charge shielding effect of **PEG.** However, the extensive grafting of PEI with **PEG** was shown to inhibit the DNA condensation process, significantly decreasing transfection efficiency. In in vitro transfection expts. with angiogenic endothelial cells, PEI-g-1PEG-RGD showed an approx. fivefold increase in transfection efficiency over PEI, due to an integrin-mediated internalization pathway. PEI-g-1PEG-RGD also exhibited high specificity to angiogenic endothelial cells compared with normal endothelial cells, which was confirmed by in vitro transfection expts. with non-targeting PEI-g-1PEG-RAE in angiostatic endothelial cells.
ST endothelial gene transfer RGD peptide **PEG** polyethylenimine conjugate
IT Angiogenesis
Human
Particle size
Transformation, genetic
Zeta potential
(angiogenic endothelial-cell-targeted polymeric gene carrier)
IT Drug delivery systems
(carriers; angiogenic endothelial-cell-targeted polymeric gene carrier)
IT DNA
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(complexes; angiogenic endothelial-cell-targeted polymeric gene carrier)
IT Blood vessel
(endothelium; angiogenic endothelial-cell-targeted polymeric gene carrier)
IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(αvβ3; angiogenic endothelial-cell-targeted polymeric gene carrier developed by conjugating an αvβ3/αv.beta .5 integrin-binding RGD peptide)
IT Integrins

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(αvβ5; angiogenic endothelial-cell-targeted polymeric gene carrier developed by conjugating an αvβ3/αv.beta .5 integrin-binding RGD peptide)

IT 9002-98-6 174459-58-6 550376-36-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(angiogenic endothelial-cell-targeted polymeric gene carrier)

IT 174459-58-6DP, RGD peptide conjugates, polyethylenimine graft derivs.
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(angiogenic endothelial-cell-targeted polymeric gene carrier)

IT 9002-98-6DP, graft polymers with **polyethylene glycol** /RGD peptide conjugates
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(angiogenic endothelial-cell-targeted polymeric gene carrier)

RE.CNT 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L100 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:886534 HCAPLUS
DN 136:32636
ED Entered STN: 07 Dec 2001
TI Method and composition for targeting an adenoviral vector
IN Wickham, Thomas J.; Kovesdi, Imre; Roelvink, Petrus W.; Einfeld, David; Brough, Douglas E.; Lizonova, Alena
PA Genvec, Inc., USA
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-86
ICS C07K014-705
CC 3-1 (Biochemical Genetics)
Section cross-reference(s): 1, 6, 10
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001092549	A2	20011206	WO 2001-US17391	20010530
	WO 2001092549	A3	20030116		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1301612	A2	20030416	EP 2001-939660	20010530
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003534806	T2	20031125	JP 2002-500741	20010530
	US 2003099619	A1	20030529	US 2002-304160	20021125
PRAI	US 2000-208451P	P	20000531		
	US 2000-631191	A2	20000802		
	WO 2001-US17391	W	20010530		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001092549	ICM	C12N015-86
	ICS	C07K014-705
US 2003099619	ECLA	C12N015/86F8

AB The invention provides adenoviral coat proteins comprising various non-native ligands. Further, the present invention provides an adenoviral vector that elicits less reticulo-endothelial system (RES) clearance in a host animal than a corresponding wild-type adenovirus. Also provided by the invention is a system comprising a cell having a non-native cell-surface receptor and a virus having a non-native ligand, wherein the non-native ligand of the virus binds the non-native cell-surface receptor of the cell. Using this system, a virus can be propagated. Further provided by the invention is a method of controlled gene expression utilizing selectively replication competence, a method of assaying for gene function, a method of isolating a nucleic acid, and a method of identifying functionally related coding sequences. Addnl., the invention provides a cell-surface receptor, which facilitates internalization.
ST adenovirus vector coat protein cell surface receptor

IT CD antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(13; method and composition for targeting an adenoviral vector)
IT Antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(17-1A; method and composition for targeting an adenoviral vector)
IT Lymphoma
(B-cell; method and composition for targeting an adenoviral vector)
IT Antigen receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CEA (carcinoembryonic antigen); method and composition for targeting an adenoviral vector)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ERBB2; method and composition for targeting an adenoviral vector)
IT Prostate-specific antigen
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(PSMA; method and composition for targeting an adenoviral vector)
IT Antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TAG-72 (tumor-associated glycoprotein 72); method and composition for targeting an adenoviral vector)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(VI or IIIa; method and composition for targeting an adenoviral vector)
IT Genome
(adenoviral, deletions of E1a and E1b regio; method and composition for targeting an adenoviral vector)
IT Viral vectors
(adenovirus; method and composition for targeting an adenoviral vector)
IT Ligands
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(binds to non-native cell-surface receptor; method and composition for targeting an adenoviral vector)
IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cell surface, non-adenoviral receptor; method and composition for targeting an adenoviral vector)
IT Reticuloendothelial system
(clearance; method and composition for targeting an adenoviral vector)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(coat; method and composition for targeting an adenoviral vector)
IT Extracellular matrix
(component; method and composition for targeting an adenoviral vector)
IT Gene
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(expression; method and composition for targeting an adenoviral vector)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(fiber, non-native ligand conjugated to; method and composition for targeting an adenoviral vector)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(function, assay of; method and composition for targeting an adenoviral vector)
IT Protein motifs
(glycerol-phosphate-inositol linkage, of non-adenovirus cell-surface receptor; method and composition for targeting an adenoviral vector)
IT Envelope proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gp120env; method and composition for targeting an adenoviral vector)
IT Proteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hexon; method and composition for targeting an adenoviral vector)
IT Biological transport
(internalization, of adenoviral vector, by cell-surface receptor; method and composition for targeting an adenoviral vector)
IT **Polyoxyalkylenes**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(lipid deriv of; method and composition for targeting an adenoviral vector)
IT Lipoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(low-d., cytoplasmic domain; method and composition for targeting an adenoviral vector)
IT Pituitary hormone receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(melanocortin receptor; method and composition for targeting an adenoviral vector)
IT Proteoglycans, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(melanoma; method and composition for targeting an adenoviral vector)
IT Antitumor agents
Drugs
Gene therapy
Human immunodeficiency virus 1
Molecular cloning
Protein sequences
Transcription, genetic
(method and composition for targeting an adenoviral vector)
IT Antibodies and Immunoglobulins
Atrial natriuretic peptide receptors
CD40 (antigen)
DNA
Endoglins
Epidermal growth factor receptors
Erythropoietin receptors
Fusion proteins (chimeric proteins)
Interleukin 1 receptors
MPL receptor
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method and composition for targeting an adenoviral vector)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(non-native cell surface receptor; method and composition for targeting an adenoviral vector)
IT Immunoglobulin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(of B cell lymphomas, antigene binding site of; method and composition for targeting an adenoviral vector)
IT Animal tissue
(of transgenic animal; method and composition for targeting an adenoviral vector)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pIX; method and composition for targeting an adenoviral vector)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(penton base; method and composition for targeting an adenoviral vector)
IT Epoxy group
(**polyethylene glycol** having; method and composition for targeting an adenoviral vector)
IT Diglycerides
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**polyethylene glycol** having; method and composition for

targeting an adenoviral vector)
IT Amines, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(primary, **polyethylene glycol** having; method and composition for targeting an adenoviral vector)
IT Melanoma
(proteoglycan; method and composition for targeting an adenoviral vector)
IT Adenoviridae
Human coxsackievirus
(receptor; method and composition for targeting an adenoviral vector)
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(recombinant, adenoviral coat protein; method and composition for targeting an adenoviral vector)
IT DNA formation
(replication, adenoviral vector; method and composition for targeting an adenoviral vector)
IT Animal
(transgenic; method and composition for targeting an adenoviral vector)
IT Protein motifs
(transmembrane domain; method and composition for targeting an adenoviral vector)
IT Infection
(viral; method and composition for targeting an adenoviral vector)
IT Cell
(with non-native cell-surface receptor; method and composition for targeting an adenoviral vector)
IT Virus
(with non-native ligand; method and composition for targeting an adenoviral vector)
IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(αv; method and composition for targeting an adenoviral vector)
IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(αvβ3; method and composition for targeting an adenoviral vector)
IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(αvβ5, cytoplasmic domain of; method and composition for targeting an adenoviral vector)
IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(αvβ6; method and composition for targeting an adenoviral vector)
IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α4; method and composition for targeting an adenoviral vector)
IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α5; method and composition for targeting an adenoviral vector)
IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α6; method and composition for targeting an adenoviral vector)
IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α9; method and composition for targeting an adenoviral vector)
IT **153477-08-8** 168179-57-5 171491-79-5 172889-42-8
174846-20-9 182574-11-4 189023-64-1 192211-05-5 211106-37-5
216763-24-5 222557-93-9 239116-04-2 239116-07-5 241478-23-9
241478-24-0 243961-35-5 243961-37-7 243961-38-8 243961-75-3
248915-60-8 255060-05-0 359636-54-7 380436-73-7 380437-46-7
380440-49-3 380440-65-3 380440-87-9 380441-27-0 380441-46-3
380441-64-5 380441-65-6
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL

(Biological study)
(amino acid sequence; method and composition for targeting an adenoviral vector)

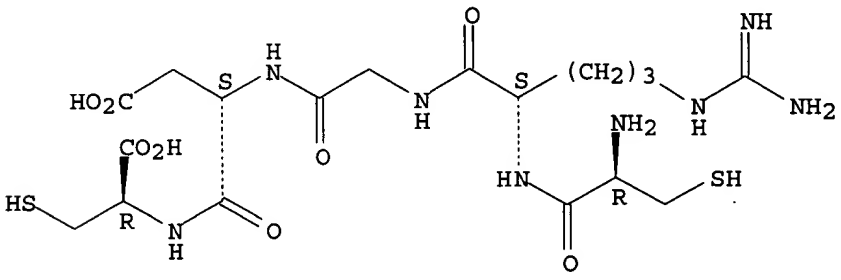
IT **25322-68-3, Polyethylene glycol**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(lipid deriv of; method and composition for targeting an adenoviral vector)

IT 9031-99-6, Membrane dipeptidase 141907-41-7, Matrix metalloproteinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method and composition for targeting an adenoviral vector)

IT **153477-08-8**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; method and composition for targeting an adenoviral vector)

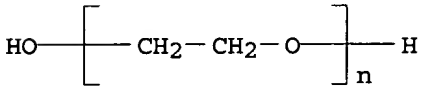
RN 153477-08-8 HCAPLUS
CN L-Cysteine, L-cysteinyl-L-arginylglycyl-L-α-aspartyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **25322-68-3, Polyethylene glycol**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(lipid deriv of; method and composition for targeting an adenoviral vector)

RN 25322-68-3 HCAPLUS
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



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L130 ANSWER 1 OF 6 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2004-224168 [21] WPIX
CR 1999-045180 [04]; 1999-045181 [04]; 2001-514378 [56]; 2003-208921 [20]; 2003-777168 [73]
DNC C2004-088394
TI Formulation useful for treating e.g. cancer comprising **camptothecin** analog and stabilizing agent.
DC A14 A23 A25 A96 B07
IN LABELL, R Y; PIGMAN, E A; **RAMASWAMI, V**; **ROMANOWSKI, M J**; **UNGER, E C**; ZUTSHI, R
PA (LABE-I) LABELL R Y; (PIGM-I) PIGMAN E A; (RAMA-I) RAMASWAMI V; (ROMA-I) ROMANOWSKI M J; (UNGE-I) UNGER E C; (ZUTS-I) ZUTSHI R
CYC 1
PI US 2004009229 A1 20040115 (200421)* 27 A61K031-4745 <--
ADT US 2004009229 A1 **CIP of US 2000-478124 20000105, CIP of US 2000-703484 20001031**, CIP of US 2001-912609 20010725, CIP of US 2002-165867 20020606, US 2003-457068 20030605
PRAI US 2003-457068 20030605; **US 2000-478124 20000105**; **US 2000-703484 20001031**; US 2001-912609 20010725; US 2002-165867 20020606
IC ICM A61K031-4745
ICS A61K009-14
AB US2004009229 A UPAB: 20040520
NOVELTY - A pharmaceutical formulation comprises a **camptothecin** analog (a), stabilizing agent (b) which stabilizes (a) but does not covalently bind to itself, optional targeting ligand (c) and an optional excipient (d).
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for preparation of the formulation comprising:
(i) mixing (a) and (b) in a solvent; and
(ii) removing the solvent to provide a dry formulation, followed by rehydration.
ACTIVITY - Cytostatic.
The antitumor efficacy of a formulation comprising 7-ethyl-10-hydroxyl **camptothecin** (A) (1.69 mg) was determined in a culture of HT-29 human colon adenocarcinoma cells. The mean tumor weight of (A) at 11 and 32 days was less than 400 and less than 200 respectively.
MECHANISM OF ACTION - Topoisomerase I inhibitor.
USE - For delivering drug useful for treating cancer (claimed).
ADVANTAGE - The formulation increases the systemic bioavailability of **camptothecin** derivatives, and is better tolerated by elderly and sick patients with fewer side effects. The lyophilized form of the formulation has improved storage stability.
Dwg.0/2
FS CPI
FA AB; GI; DCN
MC CPI: A12-V01; B04-B01B; B04-C03; B05-B01P; B06-E05; B10-E04C; B10-E04D; B14-D09; B14-H01
TECH UPTX: 20040326
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The solvent is

removed by lyophilization or spray drying. Step ii) involves removal of solvent by rotary evaporation, to provide an agglomerated intermediate product and further deagglomerating the intermediate. The solute is supercritical fluid, e.g. liquid carbon dioxide. Prior to step i), (a) is dissolved in first solvent to form first solution and (b) is dissolved in second solvent to form second solution, followed by mixing of first and second solutions. During rehydration an additional (b1) (preferably poloxamer and/or poloxamine) is added.
Preferred Formulation: The formulation is an aqueous suspension containing an acoustically active gas, or particulate having particle size of 1 - 1000 (preferably 50 - 800) nm. The formulation further comprises an aqueous vehicle selected from water, isotonic diluent or a buffer solution.
TECHNOLOGY FOCUS - POLYMERS - Preferred Components: (b) Is polymer, lipid and/or polymer-lipid conjugate (preferably linear or branched block copolymer such as **polyethylene glycol**-polypropylene oxide, **polyethylene glycol**-polylactide, **polyethylene glycol**-polylactide-coglycolide or **polyethylene glycol**-b-**polycaprolactone** copolymers, having central core and 3 - 12 arms radiating from it, where each arm comprises block copolymer with inner, more hydrophobic or hydrophilic and outer more hydrophilic or hydrophobic block). The polymer is **polyethylene glycol**, polyglycolide, polyvinyl alcohol, polyvinyl pyrrolidone, polylactide, poly(lactide-co-glycolide), **polycaprolactone**, polysorbate, **polyethylene oxide**, polypropylene oxide, **poly(ethylene oxide**-co-propylene oxide), poloxamer, poloxamine, poly(oxyethylated)glycerol, poly(oxyethylated)sorbitol and/or poly(oxyethylated)glucose or its derivatives or copolymer (preferably **polyethylene glycol** or polypropylene glycol or their copolymer having hydrolyzable linkage, poloxamer, poloxamine (especially branched and/or linear **polyethylene glycol** or its copolymer, and is optionally bound to at least one phospholipid moiety), or polysorbate). The **polyethylene glycol** is functionallized to contain at least one sulfhydryl, amino, lower alkoxy, carboxylate or phosphonate and is bound to phospholipid. The size of **polyethylene glycol** is 350 - 7000 (preferably 750 - 5000) daltons. The weight ratio of lipid to drug in (b) is less than 5:1 (preferably less than 3:1).

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The lipid is natural, chemical and enzyme modified, or synthetic phospholipid or fatty acid (preferably natural, synthetic or diacyl phospholipid, most preferably diacyl phospholipid, especially diacyl phosphatidylcholine, diacyl phosphatidylethanolamine, diacyl phosphatidylserine, diacyl phosphatidylinositol, diacyl phosphatidic acid and/or phosphorylated diacylglyceride (most preferably phosphorylated diacylglyceride selected from dioleoyl phosphatidylglycerol and/or palmitoyloleyl phosphaditylglycerol; diacyl phosphatidylcholine selected from palmitoyloleoyl phosphatidylcholine, dioleoyl phosphatidylcholine, dilauroyl phosphatidylcholine, dimyristoyl phosphaditylcholine, dipalmitoyl phosphatidylcholine and/or distearoyl phosphaditylcholine, or diacyl phosphaditylethanolamine selected from dipalmitoyl phosphaditylethanolamine, 1-palmitoyl-2-oleoylphosphaditylethanolamine and/or dioleylphosphaditylethanolamine)).
(d) Is polyhydroxyalcohol, saccharide, liquid **polyethylene glycol**, propylene glycol, glycerol and/or ethyl alcohol.
Preferred Compound: **Camptothecin** analog is of formula (I).
R1 = T (preferably 1-6C alkyl);
R2, R4, R5 = T (preferably H);
R3 = T (preferably OH); and
T = H, 1-6C alkyl, 1-6C alkoxy, acyloxy, OH, sulfhydryl, acyl, halo, amido, 1-6C alkylamido, amino, nitro or CN.

ABEX UPTX: 20040326
SPECIFIC COMPOUNDS - One compound (a) is specifically claimed, i.e. 7-ethyl-10-hydroxyl **camptothecin** (A).

ADMINISTRATION - Administration is oral, intravenous, parenteral (claimed) (e.g. subcutaneous, intramuscular, intra-arterial, intrathecal, or intraperitoneal injection), topical, transdermal, rectal, vaginal, by inhalation, intraocular, intranasal or sublingual.
No dosage details given.

EXAMPLE - A 7-ethyl-10-hydroxyl **camptothecin**/poloxamine formulation was prepared using the standard method of lyophilization from tert-butanol, and rehydrated in purified water. The rehydrated formulation was microfluidized, and sucrose was added after the fluidization step. Aliquots (1 ml) of the formulation were transferred to flint glass tubing vials (2 cc, 13 nm). The vials were stoppered with lyo-type rubber stoppers (13 nm) in the lyo-position and placed in a Unitop SQ Drying Stoppering chamber equipped with a Freezemobile research-scale freeze-dryer. The formulation was lyophilized. The resulting product was a yellowish cake.

L130 ANSWER 2 OF 6 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2003-777168 [73] WPIX
CR 1999-045180 [04]; 1999-045181 [04]; 2001-514378 [56]; 2003-208921 [20]; 2004-224168 [21]
DNC C2003-213705
TI Pharmaceutical formulation useful for the treatment of e.g. cancer comprises a **camptothecin** analog and a stabilizing agent that does not bind covalently to the **camptothecin** analog.
DC A96 B02 B07
IN **RAMASWAMI, V**; **ROMANOWSKI, M J**; **UNGER, E C**; LABELL, R Y; PIGMAN, E A; ZUTSHI, R
PA (RAMA-I) RAMASWAMI V; (ROMA-I) ROMANOWSKI M J; (UNGE-I) UNGER E C; (IMAR-N) **IMARX THERAPEUTICS INC**
CYC 103
PI US 2003059465 A1 20030327 (200373)* 22 A61K031-4745
WO 2003103596 A2 20031218 (200409) EN A61K000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2003238936 A1 20031222 (200445) A61K031-4745
ADT US 2003059465 A1 CIP of US 1998-75477 19980511, **CIP of US 2000-478124 20000105**, **CIP of US 2000-703484 20001031**, US 2002-165867 20020606; WO 2003103596 A2 WO 2003-US17959 20030605; AU 2003238936 A1 AU 2003-238936 20030605
FDT AU 2003238936 A1 Based on WO 2003103596
PRAI US 2002-165867 20020606; US 1998-75477 19980511; **US 2000-478124 20000105**; **US 2000-703484 20001031**
IC ICM A61K000-00; A61K031-4745
ICS A61K009-127; A61K009-14; A61K009-20
AB US2003059465 A UPAB: 20040716
NOVELTY - A pharmaceutical formulation comprises:
(1) a **camptothecin** analog (A);
(2) a stabilizing agent (B) that does not bind covalently to (A);
(3) an optional targeting agent (C); and
(4) an optional excipient (D).
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(I) the preparation of a nanoparticulate formulation of

camptothecin analog for parenteral administration comprising:
(a) mixing a solvent, (A) and (B);
(b) removing the solvent to provide a dry formulation of (A); and
(c) rehydrating the dry formulation; and
(II) a method of treating an individual suffering from cancer comprising:
(a) administering a pharmaceutical formulation containing drug-containing particles composed of (A), (B); and
(b) optionally (C) and (D); and
(c) an aqueous vehicle for parenteral administration. (D) is selected from a saccharide, liquid **polyethylene glycol**, polyhydroxyalcohol, propylene glycol, glycerol and/or ethyl alcohol.

ACTIVITY - Cytostatic; Vasotropic.

The cytostatic activity of a test formulation of SN-38 (RTM; 7-ethyl-10-hydroxyl **camptothecin**) stabilized with poloxamine (with the ratio of SN-38 (RTM):poloxamine of 2:1 was determined. A culture of HT-29 human colon adenocarcinoma cell was grown on McCoy's 5a medium containing L-glutamine, sodium bicarbonate and 10% fetal calf serum at 37 deg. C under an atmosphere of 5% CO2. Cells were collected with trypsin-EDTA and spun at 250 g. A final dilution was prepared at 5 million cells/l. Two injections (50 micro l) were given to nude mice to form tumors in upper leg region. At 7 days following inoculation, the mice were treated with the test/comparative formulations (500 micro l). The control mice were untreated. SN-38 (RTM) (1.69 mg) was dosed twice weekly. After 21 days of the treatment, the administration of the drugs was stopped and the experiments were terminated when the tumor growth reached 1 g. The mean tumor weight (mg) in test/control mice at 7, 11 and 17 days post implantation was found to be approx. 460/460, 360/640 and 280/1200 respectively.

MECHANISM OF ACTION - Topoisomerase Inhibitor.

USE - The composition is used for delivering a **camptothecin** drug 7-ethyl-10-hydroxyl **camptothecin** to a mammal in the treatment of cancer (claimed). Also useful as packing materials for wound and fractures and as coating materials for endoprostheses to provide local drug delivery following coronary intervention e.g. to prevent or inhibit restenosis.

ADVANTAGE - The composition has enhanced systemic bioavailability. The noncovalent drug/polymer complex allows for the formation of nanoparticles that can be suspended in an aqueous solution without requiring chemical modification of the **camptothecin** analog. The nanoparticle solubilization technology allows the preparation of **camptothecin** analog formulations with decreased toxicity and improved efficacy, while avoiding the problems related to stability, carrier toxicity and large injection volumes of currently available formulations of **camptothecin** analogs.

Dwg.0/2

FS CPI
FA AB; GI; DCN
MC CPI: A03-A01; A05-H01B; A12-V01; B04-C03; B06-E05; B12-M03; B12-M06; B14-D09; B14-F01G; B14-H01
TECH UPTX: 20040326

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Formulation: The formulation is in the form of an aqueous suspension and further comprises an aqueous vehicle selected from water, an isotonic diluent or a buffer solution and an acoustically active gas; or a particulate comprising particles having an average size of 1 nm - 1 microns (preferably 30-250 nm).

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: (B) comprises a polymer and/or a lipid.
The polymer is branched polymer, **polyethylene glycol**, polyglycolide, polyvinylalcohol, polyvinyl pyrrolidone, polylactide, poly(lactide-co-glycolide), polysorbate, **polyethylene**

oxide, polypropylene oxide, **poly(ethylene oxide**-co-propylene oxide), poloxamer, poloxamine, poly(oxyethylated) glycerol, poly(oxyethylated) sorbitol, poly(oxyethylated) glucose, their derivatives and/or copolymers (preferably poloxamer, poloxamine, **polyethylene glycol** or polypropylene glycol, especially branched **polyethylene glycol**, star **polyethylene glycol** and/or linear **polyethylene glycol** optionally covalently bound to a phospholipid moiety).
The **polyethylene glycol** is functionalized to contain at least one sulfhydryl, amino, lower alkoxy, carboxylate or phosphonate moiety and contains a hydrolyzable linkage.
The **polyethylene glycol** has a size (Daltons) of 350-7000 (preferably 750-5000).
The optional excipient is selected from saccharides or liquid **polyethylene glycols.**

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The lipid is selected from natural phospholipid, chemically or enzymatically modified phospholipid or synthetic phospholipid (preferably a natural or synthetic phospholipid, especially diacyl phosphatidyl choline, diacyl phosphatidylethanolamine, diacyl phosphatidyl serine, diacyl phosphatidylinositol, diacyl phosphatidic acid and/or phosphorylated diacylglyceride; particularly phosphorylated diacylglyceride).
The stabilizing agent is selected from palmitoyloleoyl phosphatidyl glycerol, dipalmitoyl phosphatidylethanolamine and/or 1-palmitoyl-2-oleoylphosphatidyl-ethanolamine.
The diacyl phosphatidylcholine is palmitoyl-oleoyl phosphatidylcholine, dioleyl phosphatidylcholine, dilauroyl phosphatidylcholine, dimyristoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine and/or distearoyl phosphatidylcholine.
The optional excipient is selected from polyhydroxyalcohol, propylene glycol, glycerol and/or ethyl alcohol.
(A) is of formula (i).
R1 = T (preferably 1-6C alkyl);
R2, R4, R5 = T (preferably H);
R3 = T (preferably hydroxyl, sulfhydryl or amino, especially hydroxyl);
T = H, 1-6C alkyl, 1-6C alkoxy, acyloxy, hydroxyl, sulfhydryl, acyl, halo, amido, 1-6C alkylamido, amino, nitro or cyano;
R1+R2 and R3+R4 = optionally substituted 5 or 6 membered cyclic group containing up to 2 heteroatoms selected from O, S or N.
Preferred Method: The solvent is removed by lyophilization, spray drying, or rotary evaporation to provide an agglomerated intermediate product, which is further deagglomerated.
Prior to step (I), the method involves a step of dissolving (A) in a first solvent to form a first solution and dissolving (B) in a second solvent to form a second solution, and the step (I) involves mixing the first solution and the second solution.
An additional component of (B) (preferably poloxamer and/or poloxamine) is added during step (III).

ABEX UPTX: 20040326
SPECIFIC COMPOUNDS - The **camptothecin** analog (A) is 7-ethyl-10-hydroxyl **camptothecin.**

ADMINISTRATION - The administration is orally, parenterally, intravenously (claimed), intraperitoneally, intramuscularly, intraarterially, intrathecally, transdermally, rectally, vaginally, topically, intraocularly, subcutaneously, via injection into a body cavity such as a joint, by inhalation or via an implanted reservoir (for sustained release subcutaneous or intramuscular administration). No dosage is given.
EXAMPLE - Dioleoylphosphatidylglycerol (DOPG) (120 mg) was dissolved with tert-butanol (40 ml) by heating for few minutes. SN-38 (RTM; 7-ethyl-10-hydroxyl **camptothecin**) stock solution (0.5 mg/ml) in

dichloromethane was added to the DOPG solution until a concentration of SN-38 of 1 mg/ml was obtained. Dichloromethane was removed by heating for 15 minutes and the mixture was flash-frozen with liquid nitrogen and freeze-dried overnight, to obtain poloxamine-stabilized composition of SN-38, (TETRONIC 908 (RTM; poloxamine) and DOPG, with a ratio of SN-38:DOPG:poloxamine of 2:8:1). The formulation was then rehydrated with unbuffered poloxamine solution (0.5 g poloxamine in 1 l of water) and allowed to stand for 30-60 minutes, with occasional shaking, until no large clumps of the material were present. A microfluidizer was rinsed with the rehydration solution to fill 5 ml of the microfluidizer dead volume and achieve 30 ml final formulation rehydration volume, for 20 minutes at a pressure of 50 psig to obtain poloxamine-stabilized composition.

L130 ANSWER 3 OF 6 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2003-208921 [20] WPIX
CR 1999-045180 [04]; 1999-045181 [04]; 2001-514378 [56]; 2003-777168 [73]; 2004-224168 [21]
DNC C2003-053091
TI Targeted delivery system comprising a bioactive agent homogeneously dispersed in a targeted matrix is especially useful in cancer therapy.
DC A96 B04 B05 B07 D16 P34
IN **MATSUNAGA, T O**; **RAMASWAMI, V**; **ROMANOWSKI, M J** ; **UNGER, E C**
PA (MATS-I) MATSUNAGA T O; (RAMA-I) RAMASWAMI V; (ROMA-I) ROMANOWSKI M J; (UNGE-I) UNGER E C; (IMAR-N) **IMARX THERAPEUTICS INC**
CYC 100
PI US 2002041898 A1 20020411 (200320)* 46 A61K009-14 <--
WO 2003009881 A2 20030206 (200321) EN A61M000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
AU 2002330886 A1 20030217 (200452) A61K009-14
ADT US 2002041898 A1 **CIP of US 2000-478124 20000105**, CIP of US 2000-703474 20001031, US 2001-912609 20010725; WO 2003009881 A2 **WO 2002-US22753 20020718**; AU 2002330886 A1 AU 2002-330886 20020718
FDT AU 2002330886 A1 Based on WO 2003009881
PRAI US 2001-912609 20010725; **US 2000-478124 20000105**; US 2000-703474 20001031
IC ICM A61K009-14; A61M000-00
ICS A61K039-395
AB US2002041898 A UPAB: 20040813
NOVELTY - A composition comprising a bioactive agent homogeneously dispersed in a targeted matrix (polymer and targeting ligand), is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a targeted matrix for use as a delivery vehicle comprising a polymer associated with a targeting ligand;
(2) enhancing the bioavailability of an agent comprising administration of the composition; and
(3) treating cancer comprising administration of the novel composition.
ACTIVITY - Cytostatic.
No biological data is given.
MECHANISM OF ACTION - None given.
USE - The method is useful for targeted delivery of a drug, especially in cancer therapy.
Dwg.0/5
FS CPI GMPI
FA AB; DCN

MC CPI: A12-V01; B03-L; B04-C01; B04-C02; B04-C03; B04-E01; B04-H01; B04-J01; B04-J02; B04-N04; B04-N06; B06-A03; B06-E05; B12-M10; B14-H01B; D05-H10

TECH UPTX: 20030324

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The polymer is polyalkylene oxide, polyalkylene imine, polyalkylene amine, polyalkylene sulfide, polyalkylene sulfonate, polyalkylene sulfone, poly(alkylenesulfonylalkyleneimine) or their copolymers, especially **polyethylene glycol** or a polypeptide. The polymer is **polyethylene glycol**, polypropylene glycol, branched polyethylene imine, polyvinyl pyrrolidone, polylactide, poly(lactide-co-glycolide), polysorbate, **polyethylene oxide**, **poly(ethylene oxide** -co-propylene oxide), poly(oxyethylated)glycerol, poly(oxyethylated) sorbitol, poly(oxyethylated) glucose, polymethloxazoline, polyethyloxazoline, polyvinyl alcohol, poly(hydroxyalkylcarboxylic acid) polyhydroxyethyl acrylic acid, polyhydroxypropyl methacrylc acid, polyhydroxyvalerate, polyhydroxybutyrate, polyoxazolidine, poyaspartamide, polysialic acid, linear poypropylene imine, polyethylene sulfide, polypropylene sulfide, polyethylenesulfonate, polypropylenesulfonate, polyethylene sulfone, polyethylenesulfonylethyleneimine, **polycaprolactone**, polypropylene oxide, polyvinylmethylether, polyhydroxyethyl acrylate, polyhydroxypropyl methacrylate, polyphosphazene or a derivative or mixture of them. The active agent is an anti-cancer agent, preferably paclitaxel, docetaxel, **camptothecin** or a derivative, which has limited water solubility. The targeting ligand is a protein, peptide, cytokine, growth factor, vitamin, polysaccharide, glycopeptide, glycoprotein, steroid, hormone, cofactor, bioactive agent, genetic material, drug molecule and antagonist of the GPIIBIIIA receptor of platelets which targets cells or receptors associated with the brain, kidney, lung, skin, pancreas, intestine, uterus, adrenal gland or retina. The peptide is an Abaecin, Apidaecin, AS, Bactenecin, Bac, Bactericidin, Bacteriocin, Bombinin, Bombolitin, BPTI, Brevinin, Cecropin, Charybdtoxin, Coleoptericin, Crabolin, alpha-defensin, beta-defensin, Defensin-insect, Defensin-scorpion, Dermaseptin, Diptericin, Drosocin, Esculentin, Indolicidin, Lactoferricin, Lantibiotic, Leukocon, Magainin, Mastoparan, Melittin, Phormicin, Polyphemusin, Protegrin, Royalisin, Sarcotoxin, Seminal plasmin, Tachyplesin, Thionin or Toxin.

ABEX UPTX: 20030324

SPECIFIC PEPTIDES - Specifically claimed as the targeting ligand are 43 3-21 residue amino acid sequences, e.g. Cys-Arg-Gly-Asp-Cys, Ser-Trp-Cys-Glu-Pro-Gly-Trp-Cys-Arg, and Cys-Ser-Phe-Gly-Arg-Gly-Asp-Ile-Arg-Asn-Cys.

ADMINISTRATION - 0.1-1000 mg, preferably orally, parenterally, topically, rectally or by inhalation.

EXAMPLE - **Polyoxyethylene**-sorbitan monooleate (955.6 mg) was dissolved in tert-butanol (30 ml) at 55 degrees C and paclitaxel (317.4 mg) was added. The mixture was lyophilized and the residue was treated with water (20 ml). The hydrated material was dispersed with a microfluidizer to give nanoparticles of paclitaxel in a polysorbate matrix with an average particle size of 63 nm.

L130 ANSWER 4 OF 6 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2001-514378 [56] WPIX

CR 1999-045180 [04]; 1999-045181 [04]; 2003-208921 [20]; 2003-777168 [73]; 2004-224168 [21]

DNC C2001-153657

TI Compositions for enhancing bioavailability of drugs having low aqueous solubility comprise a matrix of spatially stabilized hydrophilic polymer physically entrapping the drug within the matrix.

DC A96 B05 B07 D16

IN **ROMANOWSKI, M J; UNGER, E C**
PA (IMAR-N) **IMARX THERAPEUTICS INC**
CYC 23
PI WO 2001049268 A1 20010712 (200156)* EN 80 A61K009-14
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
W: AU CA JP
AU 2001024585 A 20010716 (200169)
EP 1246608 A1 20021009 (200267) EN A61K009-14
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
JP 2003520210 W 20030702 (200352) 94 A61K031-337
ADT WO 2001049268 A1 WO 2000-US35322 20001221; AU 2001024585 A AU 2001-24585 20001221; EP 1246608 A1 EP 2000-988371 20001221, WO 2000-US35322 20001221; JP 2003520210 W WO 2000-US35322 20001221, JP 2001-549636 20001221
FDT AU 2001024585 A Based on WO 2001049268; EP 1246608 A1 Based on WO 2001049268; JP 2003520210 W Based on WO 2001049268
PRAI **US 2000-703484 20001031; US 2000-478124 20000105**
IC ICM A61K009-14; A61K031-337
ICS A61K009-10; A61K009-127; A61K009-19; A61K031-4745; A61K038-00; A61K047-10; A61K047-28; A61K047-30; A61K047-32; A61K047-34; A61K047-42; A61K047-44; A61P035-00
AB WO 200149268 A UPAB: 20040520
NOVELTY - A composition comprising a matrix of a spatially stabilized hydrophilic polymer, a drug physically entrapped within the matrix and optional stabilizing agents, targeting ligands and excipients, is new.
DETAILED DESCRIPTION - A composition comprising a matrix of a spatially stabilized hydrophilic polymer (optionally covalently bound to a phospholipid group), a drug (which is more soluble in **polyethylene glycol** 400 than water) physically entrapped within the matrix and optional stabilizing agents, targeting ligands and excipients.
INDEPENDENT CLAIMS are included for the following:
(1) a method for treating cancer comprising parenteral administration of the composition;
(2) a method for treating cancer comprising oral administration of the composition;
(3) an improved method for administering a drug to enhance bioavailability comprising administration of the composition.
ACTIVITY - Cytostatic. No biodata is given.
MECHANISM OF ACTION - P-glycoprotein inhibitor (claimed).
USE - The composition is useful for improving the bioavailability of drugs that have low aqueous solubility, especially anticancer drugs.
Dwg.0/11
FS CPI
FA AB; DCN
MC CPI: A12-V01; B04-C03C; B04-N05; B12-M05; B14-H01; B14-L06; D05-A01A2; D05-H
TECH UPTX: 20011001
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: The hydrophilic polymer is preferably a branched polymer comprising an inner core structure attached to an outer structure which is less hydrophobic than the inner core. It is preferably **polyethylene glycol**, polyglycolide, polypropylene glycol, polyvinyl alcohol, polyvinyl pyrrolidone, polylactide, poly(lactide-co-glycolide), polysorbate, **polyethylene oxide**, polypropylene oxide, **poly(ethylene oxide**-co-propylene oxide), poly(oxyethylated) glycerol, poly(oxyethylated) sorbitol and/or poly(oxyethylated) glucose. The inner core preferably comprises polypropylene oxide and the outer structure preferably comprises **polyethylene glycol** and copolymers of propylene oxide and **ethylene oxide.** The matrix may be comprised of a number of hydrophilic polymers that do not aggregate. The phospholipid is preferably a phosphorylated diacylglyceride, especially dipalmitoyl phosphatidylethanolamine or 1-palmitoyl-2-oleylphosphatidylethanolamine.

The drug is preferably at least 1.5 times, especially 10 times, more soluble in **polyethylene glycol** 400 as in water. The stabilizing agent is preferably cholic acid or a salt (especially sodium tauracholate, sodium cholate, sodium glycholate or sodium deoxycholate) or a protein (especially a serum protein (albumin, arnylin atrial natriuretic peptide, endothelin, endothelin inhibitor, urokinase, streptokinase, staphylokinase, vasoactive intestinal peptide, high density lipoprotein, low density lipoprotein and/or very low density lipoprotein), agglutination factor, peptide hormone, structural protein, growth factor, metabolic potentiator, nuclear binding protein, enzyme, antiviral and/or immunoglobulin). The excipient is preferably a polyhydroxyalcohol (free phospholipid (diacyl phosphatidylcholine, diacyl phosphatidylethanolamine, diacylphosphatidylserine, diacyl phosphatidylinositol, diacylphosphatidic acid or phosphorylated diacylglyceride), saccharide, liquid **polyethylene glycol**, propylene glycol, glycerol and/or ethanol). The drug is preferably an anticancer agent (especially paclitaxel, docetaxel or **camptothecin** and their derivatives and analogues), a peptide, a steroid or an antibiotic. The composition may include a P-glycoprotein inhibitor, especially cyclosporin A.

ABEX UPTX: 20011001

ADMINISTRATION - Administration is oral, parenteral, topical, transdermal, by inhalation or intra-ocular. For paclitaxel, with a continuous infusion, dosage is 140-200 mg/kg.

EXAMPLE - The **PEG** (**polyethylene glycol**) component (100 mg, PEGylated phospholipid or branched **PEG**) was dissolved in tert-butanol (10 ml) by heating to 45-60 degrees C with sonication. Optional components were added and the mixture was sonicated to give a solution. Paclitaxel (10mg) was added and dissolved with heating and sonication. The mixture was flash frozen and lyophilized. The powder obtained may be rehydrated in 1 ml saline.

L130 ANSWER 5 OF 6 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1999-610583 [52] WPIX
DNC C1999-177734
TI Nucleic acid delivery vehicles useful for transfecting and infecting a target cell.
DC A96 B04 D16
IN O'RIORDAN, C; ROMANCZUK, H; WADSWORTH, S C; O'RIORDAN, C R
PA (GENZ) GENZYME CORP
CYC 23
PI WO 9940214 A2 19990812 (199952)* EN 118 C12N015-86
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP US
AU 9926629 A 19990823 (200005)
EP 1053342 A2 20001122 (200061) EN C12N015-86
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 6287857 B1 20010911 (200154) C12N015-63
JP 2003532368 W 20031105 (200377) 125 C12N015-09
AU 2003202523 A1 20030612 (200456)# C12N015-86
ADT WO 9940214 A2 WO 1999-US2680 19990208; AU 9926629 A AU 1999-26629 19990208; EP 1053342 A2 EP 1999-906805 19990208, WO 1999-US2680 19990208; US 6287857 B1 Provisional US 1998-135092P 19981103, Provisional US 1998-107471P 19981106, CIP of WO 1999-US2680 19990208, US 1999-426680 19991025; JP 2003532368 W WO 1999-US2680 19990208, JP 2000-530625 19990208; AU 2003202523 A1 Div ex AU 1999-26629 19990208, AU 2003-202523 20030326
FDT AU 9926629 A Based on WO 9940214; EP 1053342 A2 Based on WO 9940214; JP 2003532368 W Based on WO 9940214
PRAI US 1998-107471P 19981106; US 1998-20483 19980209;
US 1998-135092P 19980209; US 1999-426680 19991025;
AU 2003-202523 20030326
IC ICM C12N015-09; C12N015-63; C12N015-86

ICS A61K047-48; A61K048-00; C07H021-04; C12N015-87
ICA A61K035-76
AB WO 9940214 A UPAB: 20011012
NOVELTY - A nucleic acid delivery vehicle (I) for transfecting and/or infecting a target cell which comprises a transgene (a) and a bifunctional complex (B) that targets the nucleic acid delivery vehicle to the cell surface, is new.

DETAILED DESCRIPTION - (B) comprises a delivery vehicle binding portion, a cell surface molecule binding portion and a linker connecting them.

An INDEPENDENT CLAIM is also included for a method of delivering a transgene to a target cell comprising contacting the cell with (I) and obtaining expression of the transgene in the target cell.

USE - (I) is used for transfecting and/or infecting a target cell. The delivery vehicle can be specifically targeted to the cell via the binding to cell surface molecules. (I) can be used to target cells, which express integrins such as, HT-29 colon carcinoma cells, lymphocytes and monocytes, blood platelets, SMC-90 human lung fibroblast, MG(63) osteosarcoma cell line, vascular endothelial cells and melanoma cells. (I) is useful for delivery of nucleic acids encoding CFTR (cystic fibrosis transmembrane regulator), - alpha 1-antitrypsin, beta -glucocerebrosidase and suicide genes.

ADVANTAGE - The construct increases the efficiency of cellular uptake of (I). The constructs also enable the transfection/infection of cells that are normally refractory to transfection/infection by targeting cell receptors that are present on such cells.

Dwg.0/19
FS CPI
FA AB; DCN
MC CPI: A12-V01; A12-W11L; B04-B04C; B04-C01; B04-C03; B04-E03E; B04-F01; B04-F11; B04-G01; B04-H06A; B04-H06G; B04-H20; B04-K01; B06-D09; B14-S03; D05-C12; D05-H12A; D05-H18
TECH UPTX: 19991210
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Transgene: (A) is chosen from nucleic acids encoding CFTR, alpha1-antitrypsin, beta-glucocerebrosidase and a suicide gene. The suicide gene is chosen from HSV thymidine kinase, modified thymidine kinase, cystine deaminase, Escherichia colinitroreductase, xanthine-guanine phosphoribosyl transferase, mammalian Pf50 2B1, purine nucleoside phosphorylase, thymidine phosphorylase, deoxycytidine kinase and Varicella Zoster virus thymidine kinase. Preferred Binding molecule: The cell surface binder binds to a cell surface molecule chosen from receptors, integrins, antigens, molecules with affinity for peptides selected by phage bipanning, negatively charged cell membrane molecules and cell surface enzymes. It is preferably an antibody directed to MHC I, beta2 microglobulin, AF20 antigen, folate receptor, FGF receptor, EGF receptor, c-kit receptor, erythrocyte growth factor receptor, VEGF receptor, polymeric immunoglobulin receptor, purinoreceptor, adenovirus receptor and bFGF receptor. Alternatively it is a ligand, that binds to a cell surface receptor, chosen from folate, transferrin, FGF, EGF, c-kit, erythrocyte growth factor, VEGF and a purine or purine analogue or bFGF. It is preferably a molecule that binds to cell surface integrins, particularly RGD-containing peptides chosen from the following: KGGCRGDMFGCGDGC; KATIRRGDALADGGAC (Bt); KPARGDSSVDGC; KGRARGDNPDGDGC (Viper); KACRGDGWCGDGC; KACPSRLDSPCGDGC; **KACDCRGDCFCGDGC**; **KCDCRGDCFGDGC.** The above are cyclic peptides. The Bt peptide is the RGD sequence found in a protein secreted from Bordetella pertusiss called pertactin. The viper sequence is the RGD sequence derived from disintegrin. The remaining peptides are of human origin. The peptides below are linear RGD sequences: GRGDSPC; **CRGDCLC**; CNRCVSGCAGRC; and CNGRC. Alternatively it is a phage-biopanned peptide whose amino acid sequence is selected from the following: TTDFYYALRALA; LPKMASVQRNLA; HETFYSMIRSLA; HDTFLYGLQRLV; LTFDQTPLTAQI; ITFNQTVTTSYM; ETFSDPLAGSSS (sss.10); SDQLASPYSHPR (sss.17);

CGSGSGSGSGSKKKKKKK (p7 poly-lysine peptide); and CGSGSGSGSGSKKKKKKKKKKKKKKKKKKKK (p21-polylysine peptide) The peptide is especially sss. 10 or sss. 17. Where it binds to a negatively charged cell membrane it is especially p7 or p21-polylysine peptide.
Preferred Linker: The linker may be a small molecule introduced into either (A) or (B), or both, where the small molecule links (B) and (A). The small molecule is a heterofunctional molecule that has both an amine reactive group and a sulfhydryl-reactive group. It is chosen from N-cuccinimidyl 3-(2-pyridyldithio)propionate (SPDP), sccinimidyloxycarbonyl-alpha-methyl-(alpha-2-pyridyldithio)toluene (SMPT), m-maleimidobenzoyl-N-hydroyxsuccinimide ester (MBS), N-succinimidyl(4-iodoacetyl)aminobenzoate (SIAB), succinimyl-4-9p-maleimidophenyl)butyrate (SMPB), N-(gamma-maleimidobutyryloxy)succinimide ester (GMBS), succinimidyl-6-(iodoacetyl)amino)hexanoate) (SIAX), succinimidyl-4(((iodoacetyl)amino)methyl) (SIAC), and p-Nitrophenyl iodoacetate (NPIA). The linker further comprises a sulfo group.
Preferred Delivery Vehicle: (I) is a virus chosen from adenovirus, retrovirus, adeno-associated virus (AAV), herpes simplex virus (HSV) and poxvirus. Where the is an adenovirus (A) binds to the adenovirus. (A) is an antibody or an antibody fragment that binds to hexon or fiber protein. Where (I) is a retrovirus, (A) binds to a retrovirus envelope glycoprotein, e.g. an antibody that binds to gp70. Where the (I) is an AAV, (A) binds to AAV coat protein, e.g. an antibody that binds to VP1, VP2 or VP3. Where (I) is HSV, (A) binds to a surface glycoprotein, e.g. an antibody that binds to gB, gC, gD, gH or gL. Where (I) is a poxvirus, (A) binds to an envelope protein. The (I) is a plasmid of a nucleic acid molecule. (A) is a cationic molecule, e.g. a polycation or cationic lipid. Preferably (I) is a lipid/plasmid complex and (A) is a molecule that binds to the lipid, e.g. an anionic molecule. (A) is chemically reactive with amine groups on the surface of (I) and is an NHS ester or tresyl. Preferably, (I) is an adenovirus and the bifunctional complex comprises a **polyethylene glycol** polymer having a chemically linked AF20 antibody on one end and an anti-fiber antibody or an NHS ester/tresyl reactive moiety on the other end. (I) is an adenovirus and the bifunctional complex comprises **polyethylene glycol** polymer comprising an NHS ester reactive moiety on one end and a vinylsulfone reactive moiety on the other end having a chemically linked sss.17 peptide, polylysine peptide (p7- or p21-polylysine peptides) or bFGF. Alternatively the **polyethylene glycol** polymer comprises a tresyl reactive moiety on one end and a maleimide reactive moiety on the other end chemically linked sss. 17 peptide, polylysine peptide (p7- or p21-polylysine peptides) or bFGF.
TECHNOLOGY FOCUS - POLYMERS - Preferred Linker: The linker is a polyalkalene polymer having an average molecular weight of 200-200000 daltons. The polyalkalene polymer is chosen from polyoxymethylene, **polyethylene glycol**'s, **polyethylene oxides**, methoxypolyethylene glycol's, polymethyl-**ethylene glycol**, polyhydroxypropylene glycol, polypropylene glycol, polymethyl propylene glycol and polyhydroxypropylene oxide. The polyalkalene polymer further comprises a chemically reactive moiety at one or both ends. The reactive moiety is chosen from NHS ester, tresyl, maleimide and vinylsulfone. The polyalkalene polymer is **polyethylene glycol.**

ABEX UPTX: 19991210

WIDER DISCLOSURE - Disclosed as new is a method of producing a delivery construct containing (I).

SPECIFIC PEPTIDES - RGD containing peptidesKGGCRGDMFGCGDGC; KATIRRGDALADGGAC (Bt); KPARGDSSVDGC; KGRARGDNPDGDGC (Viper); KACRGDGWCGDGC; KACPSRLDSPCGDGC; **KACDCRGDCFCGDGC**; **KCDCRGDCFGDGC**, linear RGD sequences: GRGDSPC; **CRGDCLC**; CNRCVSGCAGRC; and CNGRC, and phage-biopanned peptides TTDFYYALRALA; LPKMASVQRNLA; HETFYSMIRSLA; HDTFLYGLQRLV; LTFDQTPLTAQI; ITFNQTVTTSYM;

ETFSDPLAGSSS (sss.10); SDQLASPYSHPR (sss.17); CGSGSGSGSGSKKKKKKK (p7 poly-lysine peptide); and CGSGSGSGSGSKKKKKKKKKKKKKKKKKKKK, are given in the specification.

EXAMPLE - Human umbilical vascular endothelial cells (HUVEC) were infected with adenovirus (Ad2beta-gal4) in the presence of increasing amounts of a bifunctional Fab complex. Increasing the amount of bifunctional Fab led to a corresponding increase in infection of HUVEC cells suggesting that the bifunctional complex could mediate adenoviral infectivity in these cells. Expression of the transgene (beta-galactosidase) in HUVEC cells infected with Ad2-beta-bgal4 vector in the presence of a reactive bifunctional Fab complex was compared with the expression in HUVEC cells infected with Ad2-Bgal4 vector in the presence of a non-reactive bifunctional complex. The reactive bifunctional Fab complex was shown to recognize both hexon and b2-microglobulin in an ELISA format, while the non-reactive complex failed to recognize hexon in the ELISA. There was a significant increase in transgene expression (up to 4-fold over expression measured with the Ad2-bgal-4 vector alone) in HUVEC cells infected with vector in the presence of the targeting complex.

L130 ANSWER 6 OF 6 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1999-045180 [04] WPIX
CR 1999-045181 [04]; 2001-514378 [56]; 2003-208921 [20]; 2003-777168 [73]; 2004-224168 [21]
DNC C1999-014089
TI Acoustically targetted drug delivery system to provide localised release - using solid porous matrix with surfactant and solvent, applies heat or ultrasound for diagnosis and local therapy.
DC A96 B05 B07
IN **UNGER, E C**
PA (IMAR-N) **IMARX PHARM CORP**; (IMAR-N) **IMARX THERAPEUTICS INC**; (UNGE-I) UNGER E C
CYC 26
PI WO 9851282 A1 19981119 (199904)* EN 138 A61K009-10
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU BR CA CN JP KR NZ
AU 9873787 A 19981208 (199916)
EP 983060 A1 20000308 (200017) EN
R: DE FR GB IT NL
US 2001018072 A1 20010830 (200151) A61K009-14
US 2002039594 A1 20020404 (200227) A61K009-14
US 2004091541 A1 20040513 (200432) A61K009-14
ADT WO 9851282 A1 WO 1998-US9570 19980512; AU 9873787 A AU 1998-73787 19980512; EP 983060 A1 **EP 1998-921109 19980512**, WO 1998-US9570 19980512; US 2001018072 A1 Provisional US 1997-46379P 19970513, Div ex US 1998-75477 19980511, US 2001-828762 20010409; US 2002039594 A1 Provisional US 1997-46379P 19970513, US 1998-75477 19980511; US 2004091541 A1 Provisional US 1997-46379P 19970513, Div ex US 1998-75477 19980511, Cont of US 2001-828762 20010409, US 2003-622027 20030716
FDT AU 9873787 A Based on WO 9851282; EP 983060 A1 Based on WO 9851282
PRAI US 1998-75477 19980511; US 1997-46379P 19970513;
US 2001-828762 20010409; US 2003-622027 20030716
IC ICM A61K009-10; A61K009-14
AB WO 9851282 A UPAB: 20040520
A solid porous matrix, comprising a surfactant in combination with a therapeutic agent, optionally also containing a solvent and/or a gas or gaseous precursor, is new.
USE - The matrix can be used for delivering a wide variety of targeted diagnostic and therapeutic agents. Particular local areas to be targeted include the eye, prostate, lung, skin, and cancers. Disorders of the eye include retinal disease, diabetic retinopathy, macular degeneration, glaucoma, and veno-occlusive disease. Disorders of the prostate include prostate cancer and benign prostatic hyperplasia.

Autoimmune diseases include arthritis, organ transplants, and myasthenia gravis. Many other diagnostic and therapeutic agents are listed. They include e.g.: antifungals, antineoplastics, enzymes, interferons, interleukins, blood products, biological response modifiers, antiallergics, anticoagulants.
Dwg.0/1
FS CPI
FA AB; DCN
MC CPI: A12-V01; A12-V03C2; B04-B01C1; B04-C03C; B10-A22; B10-H02B; B11-C08; B12-K04C1; B12-M09; B14-G02D; B14-H01; B14-N03

=> => fil uspatfull
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HIGHEST GRANTED PATENT NUMBER: US6795973
HIGHEST APPLICATION PUBLICATION NUMBER: US2004181840
CA INDEXING IS CURRENT THROUGH 21 Sep 2004 (20040921/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 21 Sep 2004 (20040921/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2004

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>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
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>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
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>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

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>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d l143 bib abs kwic hitstr tot

L143 ANSWER 1 OF 8 USPATFULL on STN
AN 2003:145875 USPATFULL
TI Method and composition for targeting an adenoviral vector
IN Wickham, Thomas J., Germantown, MD, UNITED STATES
Kovesdi, Imre, Rockville, MD, UNITED STATES
Roelvink, Petrus W., Germantown, MD, UNITED STATES
Einfeld, David, Germantown, MD, UNITED STATES
Brough, Douglas E., Gaithersburg, MD, UNITED STATES
Lizonova, Alena, Gaithersburg, MD, UNITED STATES
PA GenVec, Inc., Gaithersburg, MD (U.S. corporation)
PI US 2003099619 A1 20030529
AI US 2002-304160 A1 20021125 (10)
RLI Continuation of Ser. No. WO 2001-US17391, filed on 30 May 2001, PENDING

Continuation-in-part of Ser. No. US 2000-631191, filed on 2 Aug 2000, PENDING
PRAI US 2000-208451P 20000531 (60)
DT Utility
FS APPLICATION
LREP LEYDIG VOIT & MAYER, LTD, TWO PRUDENTIAL PLAZA, SUITE 4900, 180 NORTH STETSON AVENUE, CHICAGO, IL, 60601-6780
CLMN Number of Claims: 74
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1842
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides adenoviral coat proteins comprising various non-native ligands. Further, the present invention provides an adenoviral vector that elicits less reticulo-endothelial system (RES) clearance in a host animal than a corresponding wild-type adenovirus. Also provided by the invention is a system comprising a cell having a non-native cell-surface receptor and a virus having a non-native ligand, wherein the non-native ligand of the virus binds the non-native cell-surface receptor of the cell. Using this system, a virus can be propagated. Further provided by the invention is a method of controlled gene expression utilizing selectively replication competence, a method of assaying for gene function, a method of isolating a nucleic acid, and a method of identifying functionally related coding sequences. Additionally, the invention provides a cell-surface receptor, which facilitates internalization.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . the vector from recognition by neutralizing antibodies or the RES or itself masks the vector. Suitable agents include, for instance, **polyethylene glycol** (**PEG**), peptides that bind serum components, and the like. Alternatively, the coat protein can be engineered to contain non-native residues that. . . conjugation by way of disulfide bonding). The vector also can be functionally linked (e.g., conjugated) to a lipid derivative of **polyethylene glycol** comprising a primary amine group, an epoxy group, or a diacylglycerol group. Without being bound by any particular theory, such. . .
CLM What is claimed is:
29. The adenoviral vector of claim 26, wherein the adenoviral vector is functionally-linked to a lipid derivative of **polyethylene glycol** having a primary amine group, an epoxy group, or a diacylglycerol group.

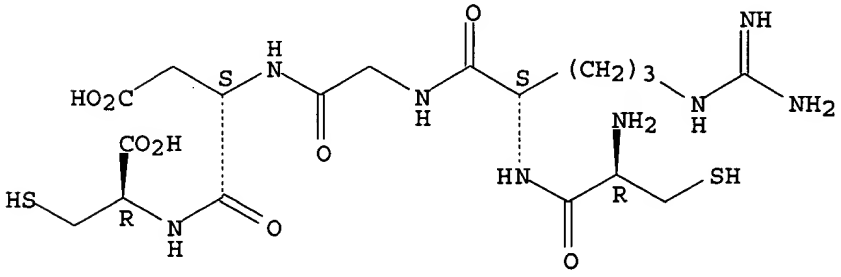
30. The adenoviral vector of claim 29, wherein the adenoviral vector is conjugated to a lipid derivative of **polyethylene glycol** having a primary amine group, an epoxy group, or a diacylglycerol group..

74. An adenoviral vector comprising a fiber protein that lacks native binding, wherein the adenoviral vector is functionally-linked to **polyethylene glycol** (**PEG**).

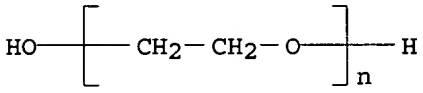
IT **Polyoxyalkylenes, biological studies**
(lipid deriv of; method and composition for targeting an adenoviral vector)
IT **153477-08-8** 168179-57-5 171491-79-5 172889-42-8
174846-20-9 182574-11-4 189023-64-1 192211-05-5 211106-37-5
216763-24-5 222557-93-9 239116-04-2 239116-07-5 241478-23-9
241478-24-0 243961-35-5 243961-37-7 243961-38-8 243961-75-3
248915-60-8 255060-05-0 359636-54-7 380436-73-7 380437-46-7
380440-49-3 380440-65-3 380440-87-9 380441-27-0 380441-46-3
380441-64-5 380441-65-6
(amino acid sequence; method and composition for targeting an adenoviral

vector)
IT **25322-68-3**, Polyethylene glycol
(lipid deriv of; method and composition for targeting an adenoviral vector)
IT **153477-08-8**
(amino acid sequence; method and composition for targeting an adenoviral vector)
RN 153477-08-8 USPATFULL
CN L-Cysteine, L-cysteinyl-L-arginylglycyl-L-α-aspartyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **25322-68-3**, Polyethylene glycol
(lipid deriv of; method and composition for targeting an adenoviral vector)
RN 25322-68-3 USPATFULL
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



L143 ANSWER 2 OF 8 USPATFULL on STN
AN 2002:287094 USPATFULL
TI Novel acoustically active drug delivery systems
IN Unger, Evan C., Tucson, AZ, UNITED STATES
PI US 2002159952 A1 20021031
AI US 2002-84855 A1 20020227 (10)
RLI Division of Ser. No. US 1998-75343, filed on 11 May 1998, PENDING
PRAI US 1997-46379P 19970513 (60)
DT Utility
FS APPLICATION
LREP Woodcock Washburn LLP, One Liberty Place - 46th Floor, Philadelphia, PA, 19103
CLMN Number of Claims: 46
ECL Exemplary Claim: 1
DRWN 9 Drawing Page(s)
LN.CNT 5458
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed to targeted therapeutic delivery systems comprising a gas or gaseous precursor filled microsphere wherein said gas or gaseous precursor filled microsphere comprises an oil, a surfactant, and a therapeutic compound. Methods of preparing the targeted therapeutic delivery systems are also embodied by the present invention which comprise processing a solution comprising an oil and a surfactant in the presence of a gaseous precursor, at a temperature below the gel to liquid crystalline phase transition temperature of the surfactant to form gas or gaseous precursor filled microsphere, and

adding to said microspheres a therapeutic compound resulting in a targeted therapeutic delivery system, wherein said processing is selected from the group consisting of controlled agitation, controlled drying, and a combination thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . al. discloses a composition with a hydrophilic polymer outer coat and a hydrophobic core polymer, the two layers linked by **polyethylene glycol.**

DETD . . . may be an aqueous liquid or an organic liquid, for example. In addition, the resuspending medium may be a cryopreservative. **Polyethylene glycol**, sucrose, glucose, fructose, mannose, trebalose, glycerol, propylene glycol, and sodium chloride may be useful as resuspending medium.

DETD . . . optionally be included in AALs from the same reference include capmul MCM, Myverol 18-92, Cremophor EL, Centrophase 31, derivatives of **polyoxyethylene**, and those disclosed in U.S. Pat. No. 5,573,781 of Brown, the disclosures of which are hereby incorporated herein by reference. . .

DETD . . . methylcellulose, and methoxycellulose. Exemplary synthetic polymers suitable for use in the present invention include polyphosphazenes, polyethylenes (such as, for example, **polyethylene glycol** (including, for example, the class of compounds referred to as Pluronics®, commercially available from BASF, Parsippany, N.J.), **polyoxyethylene**, and polyethylene terephthlate), polypropylenes (such as, for example, polypropylene glycol), polyurethanes (such as, for example, polyvinyl alcohol (PVA), polyvinyl chloride. . . ethyl acrylate, methyl methacrylate, 2-hydroxyethyl methacrylate (HEMA), lactic acid, glycolic acid, ε-caprolactone, acrolein, cyanoacrylate, bisphenol A, epichlorhydrin, hydroxyalkyl-acrylates, siloxane, dimethylsiloxane, **ethylene oxide**, **ethylene glycol**, hydroxyalkyl-methacrylates, N-substituted acrylamides, N-substituted methacrylamides, N-vinyl-2-pyrrolidone, 2,4-pentadiene-1-ol, vinyl acetate, acrylonitrile, styrene, p-amino-styrene, p-amino-benzyl-styrene, sodium styrene sulfonate, sodium 2-sulfoxyethyl-methacrylate, vinyl pyridine, aminoethyl methacrylates, 2-methacryloyloxy-trimethylammonium chloride, and polyvinylidene, as well polyfunctional crosslinking monomers such as N,N'-methylenebisacrylamide, **ethylene glycol** dimethacrylates, 2,2'-(p-phenylenedioxy)-diethyl dimethacrylate, divinylbenzene, triallylamine, polylatcidecoglycolide, polyethylene-polypropyleneglycol, and methylenebis-(4-phenylisocyanate), including combinations thereof. Preferable polymers include polyacrylic acid, polyethyleneimine, polymethacrylic acid, polymethylmethacrylate, polysiloxane, polydimethylsiloxane, polylactic acid, **poly(.epsilon .-caprolactone)**, epoxy resin, **poly(ethylene oxide)**, **poly(ethylene glycol)**, and polyamide (nylon) polymers. Preferable copolymers include the following: polyvinylidene-polyacrylonitrile, polyvinylidene-polyacrylonitrile-poilymethylmethacrylate, polystyrene-polyacrylonitrile and poly d-1, lactide co-glycolide polymers. A preferred. . .

DETD . . . Exemplary semi-synthetic polymers include carboxymethylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, methylcellulose, and methoxycellulose. Exemplary synthetic polymers include polyphosphazenes, polyethylenes (such as, for example, **polyethylene glycol** (including the class of compounds referred to as Pluronics®, commercially available from BASF, Parsippany, N.J.), **polyoxyethylene**, and polyethylene terephthlate), polypropylenes (such as, for example, polypropylene glycol), polyurethanes (such as, for example, polyvinyl alcohol (PVA), polyvinyl chloride. . .

DETD . . . molecular weight of from about 400 to about 100,000. Suitable

hydrophilic polymers are preferably selected from the group consisting of **polyethylene glycol** (**PEG**), polypropylene glycol, polyvinylalcohol, and polyvinylpyrrolidone and copolymers thereof, with **PEG** polymers being preferred. Preferably, the **PEG** polymer has a molecular weight of from about 1000 to about 7500, with molecular weights of from about 2000 to about 5000 being more preferred. The **PEG** or other polymer may be bound to the lipid, for example, DPPE, through a covalent bond, such as an amide, carbamate or amine linkage. In addition, the **PEG** or other polymer may be linked to a targeting ligand, or other phospholipids, with a covalent bond including, for example, amide, ester, ether, thioester, thioamide or disulfide bonds. Where the hydrophilic polymer is **PEG**, a lipid bearing such a polymer will be said to be "pegylated." In preferred form, the lipid bearing a hydrophilic polymer may be DPPE-**PEG**, including, for example, DPPE-PEG5000, which refers to DPPE having a **polyethylene glycol** polymer of a mean weight average molecular weight of about 5000 attached thereto (DPPE-PEG5000). Another suitable pegylated lipid is distearoylphosphatidylethanol-amine-**polyethylene glycol** 5000 (DSPE-PEG5000).

DETD . . . charged. Consequently, DPPA, which is negatively charged, may be added to enhance stabilization in accordance with the mechanism described above. DPPE-**PEG** provides a pegylated material bound to the lipid membrane or skin of the vesicle by the DPPE moiety, with the **PEG** moiety free to surround the vesicle membrane or skin, and thereby form a physical barrier to various enzymatic and other endogenous agents in the body whose function is to degrade such foreign materials. The DPPE-**PEG** may provide more vesicles of a smaller size which are safe and stable to pressure when combined with other lipids,. . . function as diagnostic imaging contrast media. A wide variety of targeting ligands may be attached to the free ends of **PEG**. The **PEG** typically functions as a spacer and improves targeting.

DETD . . . and di-glycerides, mono-ethanolamine, oleic acid, oleyl alcohol, poloxamer, for example, poloxamer 188, poloxamer 184, poloxamer 181, Pluronics® (BASF, Parsippany, N.J.), **polyoxyethylene** 50 stearate, polyoxyl 35 castor oil, polyoxyl 10 oleyl ether, polyoxyl 20 cetostearyl ether, polyoxyl 40 stearate, polysorbate 20, polysorbate. . . sodium 12, carrageenan, cellulose, dextran, gelatin, guar gum, locust bean gum, veegum, hydroxyethyl cellulose, hydroxypropyl methylcellulose, magnesium-aluminum-silicate, Zeolites®, methylcellulose, pectin, **polyethylene oxide**, povidone, propylene glycol alginate, silicon dioxide, sodium alginate, tragacanth, xanthan gum, α-d-gluconolactone, glycerol and mannitol; (iv) synthetic suspending agents, such as **polyethylene glycol** (**PEG**), polyvinylpyrrolidone (PVP), polyvinylalcohol (PVA), polypropylene glycol (PPG), and polysorbate; and (v) tonicity raising agents which stabilize and add tonicity, including,. . .

DETD . . . 5,149,543 which is incorporated herein by reference. In addition, nonionic surfactants selected from the group consisting of Triton-X® (octoxynols), Tweens® (**polyoxyethylene** sorbitans), Brij® (**polyoxyethylene** ethers), Pluronics® (**polyethylene glycol**), Zonyls® (fluorosurfactants), and Fluorads® may be useful in the present invention.

DETD . . . for example, ZONYL® surfactants identified as Telomer B, including Telomer B surfactants which are pegylated (i.e., have at least one **polyethylene glycol** group attached thereto), also known as **PEG**-Telomer B, available from the DuPont Company.

DETD . . . acid (DSPA); palmitic acid; stearic acid; arachidonic acid; oleic acid; lipids bearing polymers, such as chitin, hyaluronic acid,

polyvinylpyrrolidone or **polyethylene glycol** (**PEG**), also referred to herein as "pegylated lipids" with preferred lipid bearing polymers including DPPE-**PEG** (DPPE-**PEG**), which refers to the lipid DPPE having a **PEG** polymer attached thereto, including, for example, DPPE-PEG5000, which refers to DPPE having attached thereto a **PEG** polymer having a mean average molecular weight of about 5000; lipids bearing sulfonated mono-, di-, oligo- or polysaccharides;

DETD . . . chain of about 6 carbons and another acyl chain of about 12 carbons; ceramides; non-ionic liposomes including niosomes such as **polyoxyethylene** fatty acid esters, **polyoxyethylene** fatty alcohols, **polyoxyethylene** fatty alcohol ethers, polyoxyalkylene sorbitan fatty acid esters (such as, for example, the class of compounds referred to as TWEEN.TM., commercially available from ICI Americas, Inc., Wilmington, Del.), including polyoxyethylated sorbitan fatty acid esters, glycerol **polyethylene glycol** oxystearate, glycerol **polyethylene glycol** ricinoleate, ethoxylated soybean sterols, ethoxylated castor oil, **polyoxyethylene**-polyoxypropylene polymers, and **polyoxyethylene** fatty acid stearates; sterol aliphatic acid esters including cholesterol sulfate, cholesterol butyrate, cholesterol isobutyrate, cholesterol palmitate, cholesterol stearate, lanosterol acetate,. . .

DETD . . . amides of phosphatidyl ethanolamine such as anandamides and methanandamides, phosphatidyl serine, phosphatidyl inositol and fatty acid esters thereof, cardiolipin, phosphatidyl **ethylene glycol**, acidic lysolipids, sulfolipids, and sulfatides, free fatty acids, both saturated and unsaturated, and negatively charged derivatives thereof. Phosphatidic acid and. . .

DETD . . . salts, and ZONYL® surfactants identified as Telomer B, including Telomer B surfactants which are pegylated (i.e., have at least one **polyethylene glycol** group attached thereto), also known as **PEG**-Telomer B, may be used to stabilize the lipid and/or vesicle compositions, and to act, for example, as a coating for. . .

DETD . . . also be employed. One or more emulsifying agents may also be incorporated into the oil, such as phospholipid, fatty acids, **polyethylene glycol** or other surfactants such as pluronic, Tween, Zonyl, and the like, to aid in preparation of a homogeneous suspension of. . .

DETD [0270] With respect to **polyethylene glycol** containing fragments, the following can be used, for example, PEG2--NHS ester, NHS-**PEG**-VS, NHS-**PEG**-MAL, methoxy-**PEG** -vinylsulfone, **PEG**-(VS).sub.2, methoxy-**PEG**-ald, **PEG**-(ald).sub.2, methoxy-**PEG**-epx, **PEG** -(epx).sub.2, methoxy-**PEG**-Tres, **PEG**-(Tres).sub.2, methoxy-**PEG**-NPC.sub.2, **PEG**-(NPC).sub.2, methoxy-**PEG**-CDI, **PEG**-(CDI).sub.2, mPEG-Gly-OSu, mPEG-NLe-OSu, methoxy-SPA-**PEG**, (SPA).sub.2-**PEG**, methoxy-SS-**PEG**, (SS).sub.2-**PEG** all of which are available from Shearwater Polymers, Inc. (Huntsville, Ala.). Where these types of fragments are used, i.e., where. . .

DETD . . . fusion or agglutination from occurring. Additives which may be useful include sorbitol, mannitol, sodium chloride, glucose, dextrose, trehalose, polyvinyl-pyrrolidone and **poly(ethylene glycol)** (**PEG**), for example, **PEG** 400. These and other additives are described in the literature, such as in the U.S. Pharmacopeia, USP XNI, NF XVII,. . .

DETD . . . skilled in the art, including, for example, glycerol, propylene glycol; isopropyl myristate; urea in propylene glycol, ethanol and water; and **polyethylene glycol** (**PEG**).

DETD . . . 1 mg per ml of 82 mole percent dipalmitoylphosphatidylcholine (DPPC), 10 mole percent dipalmitoylphosphatidic acid (DPPA) and 8 mole

percent dipalmitoylphosphatidylethanolamine-**polyethyleneglycol** (DPPE-PEG5,000). All of the lipids were purchased from Avanti Polar Lipids, Alabaster, Ala. The liquid was sealed in an 2. . .

DETD [0364] The linear peptide **CRGDC** was synthesized by standard solid phase methodology using alpha amino-FMOC protection. This procedure will involve the use of the fluorenylmethoxycarbonyl. . . 2+2 minute washes of CH.sub.2Cl.sub.2. The remaining protected amino acids will be coupled in the same manner to provide the **CRGDC**-resin complex. Following binding of the FMOC-Val to the resin, further couplings will be initiated as set forth below.

DETD [0368] The peptide **CRGDC** requires only the sidechain protection of the lysines. A number of protecting group schemes are compatible with the synthetic scheme.. . . example, Boc-Lys with a fluorenylmethoxycarbonyl (FMOC) sidechain protecting group may be used to prevent the reaction of other amino acids, **PEG**, or the DPGS with the side chain group. In addition, a Boc-Asp with a β-carboxyfluorenylmethyl (OFm) ester bond may be used to protect the sidechain carboxyl. Prior to removal of the DPGS-**PEG**-**CRGDC** from the resin, mild conditions as 20% piperidine and N-methylpyrollidone can be initiated to remove both the FMOC group from. . .

DETD . . . the sidechain groups using 2% hydrazine in NMP, DMF, or CH.sub.2Cl.sub.2 for one hour. After removal of the sidechains, the DPGS-**PEG**-**CRGDC** will be washed with 2+2 min. NMP.

DETD . . . antiinflammatory drug. Dexamethasone is soluble at 100 mg/L in water. A mixture is created by adding 80 mg of a **PEG** Telomer B (DuPont, Wilmington, Del.) to 20 mg of dexamethasone. The mixture is dissolved in methanol and rotary evaporated under. . . in methanol at 237 nm peak absorbance. The standard curve is between 2.5 and 25 μg/ml. The fractions that contained **PEG** Telomer B were suspensions and may not be scanned accurately. The remaining fractions are scanned and presumably contained the free,. . . of a 10 mg/ml reconstituted solution, dissolved in methanol and measured at UV 235 nm, demonstrates that 20% of the **PEG**-Telomer B aggregate complex is dexamethasone. The experiment showed the high payload efficiency of the fluorosurfactant aggregation technique.

DETD [0372] The lyophilized material comprising dexamethasone plus fluorosurfactant (20 mgs of **PEG** Telomer B) from Example 1 is suspended in 1.5 mls of soybean oil in a Teflon coated stoppered vial. To. . .

DETD . . . of compoimds extracted from tissue. 320 μl of this solution was added to 1.5 ml of dipalmitoylphosphatidylcholine dipalmitoylphosphatidylethanolamine coupled to **polyethylene glycol** 5000, and dipalmitoylphosphatidic acid, in a ratio of about 82%:8%:10% (mole %) and the gas perfluoropropane in a 2 ml. . .

DETD . . . after IV injection of a bolus of different formulations of AALs. A comparison injection with imaging was also performed with DPPC:DPPE-**PEG**:DPPA (82%:8%: 10% (mole %)) perfluorobutane gas filled contrast agent. Formulations of AALs which were tested included vesicles with two different. . . image heart and kidney. Images were recorded on videotape. The AALs gave less robust contrast than an equivalent dose of DPPC:DPPE-**PEG**:DPPA (82%:8%: 10% (mole %)) perfluorobutane gas filed contrast agent but the duration of contrast was almost the same. Contrast could. . .

CLM What is claimed is:

. . . ganglioside GM2; glucolipids; sulfatides; glycosphingolipids; phosphatidic acid; palmitic acid; stearic acid; arachidonic acid; oleic acid; lipids bearing polymers such as **polyethyleneglycol**, chitin, hyaluronic acid or polyvinylpyrrolidone; lipids bearing sulfonated mono-, di-, oligo- or polysaccharides; cholesterol, cholesterol sulfate; cholesterol hemisuccinate; tocopherol hemisuccinate,. . .

. . . A composition of claim 3 wherein said polypeptide is selected from the group consisting of polyglutamic acid, polylysine, polyphosphazene, polyvinylalcohol, **polyethyleneglycol**, polypropyleneglycol, and a copolymer.

. . . soybean oil, said surfactant comprises 82 mol percent dipalmitoylphosphatidyl choline, 10 mol percent dipalmitoylphosphatidic acid, and 8 mol percent dipalmitoylphosphatidyl ethanolamine-**polyethylene glycol** 5000, and said gaseous precursor is perfluorobutane.

. . . soybean oil, said surfactant comprises 82 mol percent dipalmitoylphosphatidyl choline, 10 mol percent dipalmitoylphosphatidic acid, and 8 mol percent dipalmitoylphosphatidyl ethanolamine-**polyethylene glycol** 5000, and said gaseous precursor is perfluorobutane.

. . . is soybean oil, said surfactant comprises 82 mol percent dipalmitoylphosphatidyl choline, 10 mol percent dipalmitoylphosphatidic acid, 8 mol percent dipalmitoylphosphatidyl ethanolamine-**polyethylene glycol** 5000 and Pluronic F-68, and said gaseous precursor is perfluorobutane.

. . . is soybean oil, said surfactant comprises 82 mol percent dipalmitoylphosphatidyl choline, 10 mol percent dipalmitoylphosphatidic acid, 8 mol percent dipalmitoylphosphatidyl ethanolamine-**polyethylene glycol** 5000 and Pluronic F-68, and said gaseous precursor is perfluorobutane.

. . . is soybean oil, said surfactant comprises 82 mol percent dipalmitoylphosphatidyl choline, 10 mol percent dipalmitoylphosphatidic acid, 8 mol percent dipalmitoylphosphatidyl ethanolamine-**polyethylene glycol** 5000 and Pluronic F-68, and said gaseous precursor is perfluorobutane.

. . . said therapeutic is a dye, said oil is soybean oil, said surfactant comprises 82 mol percent dipalmitoylphosphatidylcholine, 8 mol percent dipalmitoylphosphatidylethanolamine-**polyethylene glycol** 5000, and 10 mol percent dipalmitoylphosphatidic acid, said gaseous precursor is perfluoropropane.

. . . A method of claim 30 wherein said therapeutic is dexamethasone, said surfactant comprises 82 mol percent dipalmitoylphosphatidylcholine, 8 mol percent dipalmitoylphosphatidylethanolamine-**polyethylene glycol** 5000, and 10 mol percent dipalmitoylphosphatidic acid, and said gas is perfluorobutane and nitrogen.

. . . A method of claim 30 wherein said therapeutic is amphotericin, said surfactant comprises 82 mol percent dipalmitoylphosphatidylcholine, 8 mol percent dipalmitoylphosphatidylethanolamine-**polyethylene glycol** 5000, and 10 mol percent dipalmitoylphosphatidic acid, and said gas is selected from perfluorobutane and nitrogen.

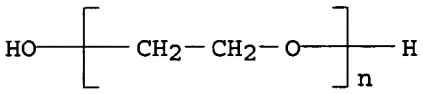
IT **Polyoxyalkylenes, biological studies**
(ethers; preparation of solid porous matrixes for pharmaceutical uses)
IT **Polyoxyalkylenes, biological studies**
(preparation of solid porous matrixes for pharmaceutical uses)
IT 646-04-8, trans-2-Pentene 661-54-1, Propyne-3,3,3-trifluoro 661-97-2 677-56-5, Propane-1,1,1,2,2,3-hexafluoro 678-26-2, Perfluoropentane 684-16-2, Hexafluoroacetone 685-63-2, Hexafluoro-1,3-butadiene 689-97-4, Vinyl acetylene 692-50-2, Hexafluoro-2-butyne 752-61-4, Digitalin 768-94-5, Amantadine 818-92-8, 3-FluoroPropylene 846-50-4, Temazepam 921-13-1, Chlorodinitromethane 927-84-4,

Trifluoromethyl peroxide 928-45-0, Butyl nitrate 968-93-4, Testolactone 987-24-6, Betamethasone acetate 990-73-8, Fentanyl citrate 1070-11-7, Ethambutol hydrochloride 1119-94-4, Lauryltrimethylammonium bromide 1119-97-7, Myristyltrimethylammonium bromide 1172-18-5 1177-87-3, Dexamethasone acetate 1191-96-4, EthylCyclopropane 1306-06-5, Hydroxylapatite 1397-89-3, Amphotericin B 1400-61-9, Nystatin 1404-04-2, Neomycin 1405-37-4, Capreomycin sulfate 1493-03-4, Difluoroiodomethane 1597-82-6, Paramethasone acetate 1630-94-0, 1,1-DimethylCyclopropane 1691-13-0, 1,2-Difluoroethylene 1722-62-9, Mepivacaine hydrochloride 1759-88-2 1867-66-9, Ketamine hydrochloride 2022-85-7, Flucytosine 2068-78-2, Vincristine sulfate 2314-97-8, IodotriFluoromethane 2366-52-1, 1-Fluorobutane 2375-03-3, Methylprednisolone sodium succinate 2392-39-4, Dexamethasone sodium phosphate 2511-95-7, 1,2-DimethylCyclopropane 2551-62-4, Sulfur hexafluoride 3116-76-5, Dicloxacillin 3385-03-3, Flunisolide 3458-28-4, Mannose 3485-14-1, Cyclacillin 3511-16-8, Hetacillin 3529-04-2, Benzyldimethylhexadecylammonium bromide 3810-74-0, Streptomycin sulfate 3858-89-7, Chloroprocaine hydrochloride 4185-80-2, Methotrimeprazine hydrochloride 4428-95-9, Foscarnet 4431-00-9, Aurintricarboxylic acid 4697-36-3, Carbenicillin 4786-20-3, Crotononitrile 4901-75-1, 3-Ethyl-3-methyldiaziridine 5534-09-8, Beclomethasone dipropionate 5536-17-4, Arabinosyl adenine 5611-51-8, Triamcinolone hexacetonide 5714-22-7, Sulfur fluoride (S2F10) 6000-74-4, Hydrocortisone sodium phosphate 7281-04-1, Benzyldimethyldodecylammonium bromide 7297-25-8, Erythritol tetranitrate 7439-89-6, Iron, biological studies 7440-01-9, Neon, biological studies 7440-06-4D, Platinum, compds., biological studies 7440-15-5, Rhenium, biological studies 7440-24-6, Strontium, biological studies 7440-26-8, Technetium, biological studies 7440-48-4, Cobalt, biological studies 7440-63-3, Xenon, biological studies 7440-65-5, Yttrium, biological studies 7601-55-0, Metocurine iodide 7637-07-2, biological studies 7647-14-5, Sodium chloride, biological studies 7681-14-3, Prednisolone tebutate 7727-37-9, Nitrogen, biological studies 7728-73-6 7782-41-4, Fluorine, biological studies 7782-44-7, Oxygen, biological studies 7783-82-6, Tungsten hexafluoride 9001-75-6, Pepsin 9001-78-9, Alkaline phosphatase 9002-01-1, Streptokinase 9002-04-4, Thrombin 9002-60-2, Adrenocorticotropic hormone, biological studies 9002-61-3 9002-72-6, Growth hormone 9002-79-3, Melanocyte stimulating hormone 9002-89-5, Poly(vinyl alcohol) 9003-11-6 9003-39-8, PVP 9004-10-8, Insulin, biological studies 9004-34-6, Cellulose, biological studies 9004-54-0, Dextran, biological studies 9004-61-9, Hyaluronic acid 9004-67-5, Methyl Cellulose 9005-25-8, Starch, biological studies 9005-27-0, HETA-starch 9005-32-7, Alginic acid 9005-49-6, Heparin, biological studies 9005-64-5, Polyoxyethylene sorbitan monolaurate 9005-65-6, Polyoxyethylene sorbitan monooleate 9005-66-7, Polyoxyethylene sorbitan monopalmitate 9005-67-8, Polyoxyethylene sorbitan monostearate 9005-71-4, Polyoxyethylene sorbitan tristearate 9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies 9011-14-7, PMMA 9011-97-6, Cholecystokinin 9015-68-3, Asparaginase 9015-71-8, Corticotropin releasing factor 9036-19-5, Octoxynol 9039-53-6, Urokinase 9061-61-4, Nerve growth factor 10024-97-2, Nitrogen oxide (N2O), biological studies 11000-17-2, Vasopressin 11056-06-7, Bleomycin 11096-26-7, Erythropoietin 13264-41-0, Cetyldimethylethylammonium chloride 13292-46-1, Rifampin 13311-84-7, Flutamide 13647-35-3, Trilostane 15500-66-0, Pancuronium bromide 15663-27-1, Cisplatin 15686-71-2, Cephalexin 15687-27-1, Ibuprofen 16009-13-5, Hemin 16136-85-9 17598-65-1, Deslanoside 18010-40-7, Bupivacaine hydrochloride 18323-44-9, Clindamycin 18378-89-7, Plicamycin 18773-88-1, Benzyldimethyltetradecylammonium bromide 20187-55-7, Bendazac 20274-91-3 20830-75-5, Digoxin 21829-25-4, Nifedipine 22204-53-1, Naproxen 22494-42-4, Diflunisal 22916-47-8, Miconazole 23110-15-8, Fumagillin 23541-50-6, Daunorubicin

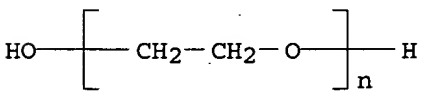
hydrochloride 24356-66-9 24764-97-4, 2-Bromobutyraldehyde
24991-23-9 25104-18-1, Polylysine 25151-81-9, Prostanoic acid
25316-40-9, Adriamycin **25322-68-3 25322-68-3D**, PEG,
ethers 25322-69-4, Polypropylene glycol 25513-46-6, Polyglutamic acid
26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] 26100-51-6,
Poly(lactic acid) 26171-23-3, Tolmetin 26780-50-7, Glycolide-lactide
copolymer 26787-78-0, Amoxicillin 26839-75-8, Timolol 28911-01-5,
Triazolam 29121-60-6, Vaninolol 29767-20-2, Teniposide 30516-87-1,
Azidothymidine 31637-97-5, Etofibrate 33069-62-4, Taxol 33125-97-2,
Etomidate 33419-42-0, Etoposide 33507-63-0, Substance p 34077-87-7,
DiChlorotrifluoroethane 34787-01-4, Ticarcillin 36322-90-4
36637-19-1, Etidocaine hydrochloride 36791-04-5, Ribavirin
38000-06-5, Polylysine 38194-50-2, Sulindac 38821-53-3, Cephradine
39391-18-9, Cyclooxygenase 41575-94-4, Carboplatin 42399-41-7,
Diltiazem 47141-42-4, Levobunolol 50370-12-2, Cefadroxil
50402-72-7, Piperidine-2,3,6-trimethyl 50700-72-6, Vecuronium bromide
50972-17-3, Bacampicillin 51264-14-3, Amsacrine 52205-73-9,
Estramustine phosphate sodium 52365-63-6, Dipivefrin 53045-71-9,
1-Pentene-3-bromo 53188-07-1, Trolox 53678-77-6, Muramyldipeptide
53994-73-3, Cefaclor 54965-24-1, Tamoxifen citrate 55142-85-3,
Ticlopidine 57223-18-4, 1-Nonen-3-yne 59277-89-3, Acyclovir
59467-96-8, Midazolam hydrochloride 60118-07-2, Endorphin 62031-54-3,
Fibroblast growth factor 62229-50-9, Epidermal growth factor
62232-46-6, Bifemelane hydrochloride 62571-86-2, Captopril
62683-29-8, Colony stimulating factor 63659-18-7, Betaxolol
65277-42-1, Ketoconazole 68302-57-8 68367-52-2, Sorbinil
69279-90-9, Ansamitocin 72702-95-5, Ponalrestat 73218-79-8,
Apraclonidine hydrochloride 73984-11-9 74381-53-6, Leuprolide acetate
74790-08-2, Spiroplatin 75847-73-3, Enalapril 76547-98-3, Lisinopril
77181-69-2, Sorivudine 80755-87-9 81486-22-8, Nipradilol
82159-09-9, Epalrestat 82410-32-0, Ganciclovir 82964-04-3, Tolrestat
83869-56-1, Granulocyte macrophage colony stimulating factor
86090-08-6, Angiostatin 88096-12-2 89149-10-0, 15-Deoxyspergualin
98023-09-7 99896-85-2 106956-32-5, Oncostatin M 113852-37-2,
Cidofovir 116632-15-6, 1.2.3-Nonadecanetricarboxylic acid
2-hydroxytrimethylester 119813-10-4, Carzelesin 120279-96-1,
Dorzolamide 120287-85-6D, Cetrorelix, derivs. 121181-53-1, Filgrastim
124389-07-7, Muramyltripeptide 127464-60-2, Vascular endothelial growth
factor
(preparation of solid porous matrixes for pharmaceutical uses)

IT **25322-68-3 25322-68-3D**, PEG, ethers
(preparation of solid porous matrixes for pharmaceutical uses)

RN 25322-68-3 USPATFULL
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



RN 25322-68-3 USPATFULL
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



L143 ANSWER 3 OF 8 USPATFULL on STN
AN 2002:192059 USPATFULL
TI NOVEL INTEGRIN-BINDING PEPTIDES
IN RUOSLAHTI, ERKKI, RANCHO SANTA FE, CA, UNITED STATES
KOIVUNEN, ERKKI, SAN DIEGO, CA, UNITED STATES
PI US 2002103130 A1 20020801
AI US 1999-364597 A1 19990730 (9)
RLI Continuation of Ser. No. US 1994-286861, filed on 4 Aug 1994, GRANTED, Pat. No. US 5981478 Continuation-in-part of Ser. No. US 1993-158001, filed on 24 Nov 1993, ABANDONED
DT Utility
FS APPLICATION
LREP CAMPBELL & FLORES LLP, 4370 LA JOLLA VILLAGE DRIVE, 7TH FLOOR, SAN DIEGO, CA, 92122
CLMN Number of Claims: 71
ECL Exemplary Claim: 1
DRWN 13 Drawing Page(s)
LN.CNT 1784
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention is directed to novel integrin binding peptides. These peptides bind to α.sub.v- of α.sub.5-containing integrins and can exhibit high binding affinity. They contain one of the following sequence motifs: RX.sub.1ETX.sub.2WX.sub.3 [SEQ ID NO: _____] (especially RRETAWA [SEQ ID NO: _____]); RGDGX [SEQ ID NO: _____], in which X is an amino acid with a hydrophobic, aromatic side chain; the double cyclic CX.sub.1CRGDCX.sub.2C [SEQ ID NO: _____]; and RLD. The peptides generally exhibit their highest binding affinity when they assume a conformationally stabilized configuration. This invention also provides methods of using these peptides.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD [0084] The cyclic peptides GACRRETAWACGA [SEQ ID NO: _____] (*CRRETAWAC*) [SEQ ID NO: _____] and GA***CRGDC***LGA [SEQ ID NO: _____] (***CRGDC***) [SEQ ID NO: _____] were synthesized using an Applied Biosystems Model 430A synthesizer (Foster City, Calif.) and purified by reverse-phase. . .
DETD . . . hours in the presence of 20 μg/ml of tetracycline, and phage were collected from the supernatant by precipitation twice with **polyethylene glycol.** The phage pellets were dissolved at approximately 10.sup.13 transducing units (TU)/ml in TBS buffer containing 0.02% NaN.sub.3 and stored at. . .
DETD [0091] Relative affinities of the CRRETAWAC [SEQ ID NO: _____] and **CRGDC** [SEQ ID NO: _____] peptides were determined by inhibition of binding of peptide-displaying phage to α.sub.5β.sub.1 integrin. Peptide-displaying phage were. . .
DETD . . . 1 hour in the presence of various concentrations of the cyclic peptides containing CRRETAWAC [SEQ ID NO: _____] and containing **CRGDC** [SEQ ID NO: _____] in microliter wells coated with the α.sub.5β.sub.1 integrin. Binding was quantitated by adding K91kan bacteria directly. . .
DETD [0093] FIG. 4 shows the inhibition of RRETAWA [SEQ ID NO: _____]-displaying phage binding to α.sub.5β.sub.1 integrin by **CRGDC** [SEQ ID NO: _____] and CRRETAWAC [SEQ ID NO: _____]. The CRRETAWAC [SEQ ID NO: _____] motif inhibited at least 10 times more efficiently than the **CRGDC** [SEQ ID NO: _____] containing peptides. A control peptide GRGESP [SEQ ID NO: _____] had no effect.
DETD . . . _____] phage were added together with various concentrations of the cyclic peptides containing CRRETAWAC [SEQ ID NO: _____] and containing **CRGDC** [SEQ ID NO: _____] into microliter wells coated with the α.sub.5β.sub.1 integrin, incubated for 1 hour at room temperature and binding to wells was quantitated. As shown in FIG. 2, the CRRETAWAC [SEQ ID NO: _____] and **CRGDC** [SEQ ID

NO: _____] inhibit the binding of ELRGDGW-displaying [SEQ ID NO: _____] phage to α.sub.5β.sub.1 integrin to approximately the. . .

DETD [0095] The ability of CRRETAWAC [SEQ ID NO: _____] and **CRGDC** [SEQ ID NO: _____] containing peptides to inhibit binding of CRGDCL-displaying [SEQ ID NO: _____] phage to the microwells coated. . .

DETD . . . in FIG. 1, the cyclic CRRETAWAC [SEQ ID NO: _____] peptide inhibits fibronectin binding equally as well as the cyclic **CRGDC** [SEQ ID NO: _____] peptide.

DETD . . . the B2/C1). This attachment was inhibited by the RRETAWA-[SEQ ID NO: _____] containing peptide (1 mM) as well as by **CRGDC** [SEQ ID NO: _____] (1 mM) and by EDTA (10 mM). The α.sub.vβ.sub.1-expressing B2/v7 cells also bound to the peptide,. . .

DETD [0113] A search for high affinity sequences yielded four sequences with the **CRGDC** [SEQ ID NO: _____] motif, each from the CX.sub.7C library. These sequences contained two additional cysteines, suggesting the presence of. . .

DETD . . . [SEQ ID NO: _____] peptide was 5-fold more active in inhibiting the binding of RGD-displaying phage to α.sub.5β.sub.1 than the * **CRGDC*** [SEQ ID NO: _____] peptide (FIG. 9). We also synthesized a peptide according to one of the RLD-containing phage. One. . .

DETD . . . disulfide bonding of the peptide. One disulfide bond is possibly formed between the cysteines flanking the RGD sequence, as the ***CRGDC*** [SEQ ID NO: _____] peptide is active. A second disulfide bridge would then form between the CX.sub.7C cysteines, although we. . .

DETD [0117] The cyclized ACDCRGDCFCG [SEQ ID NO: _____] peptide was 10-fold more potent than the single disulfide bond-containing peptide * **CRGDC*** [SEQ ID NO: _____] in inhibiting the binding of RGD-containing phage to α.sub.vβ.sub.5 (FIG. 10). Phage binding to α.sub.vβ.sub.3 was inhibited by the ACDCRGDCFCG [SEQ ID NO: _____] peptide 5-fold better than by ***CRGDC*** [SEQ ID NO: _____], indicating that the ACDCRGDCFCG [SEQ ID NO: _____] peptide binds to both of these α.sub.v integrins.. . .

DETD . . . its affinity was low. In α.sub.vβ.sub.3 and α.sub.vβ.sub.5 binding assays, the peptide had a 100-fold and 1000-fold lower activity than ***CRGDC*** [SEQ ID NO: _____], respectively. The low affinity may partially be due to the tendency of the peptide precipitate at. . .

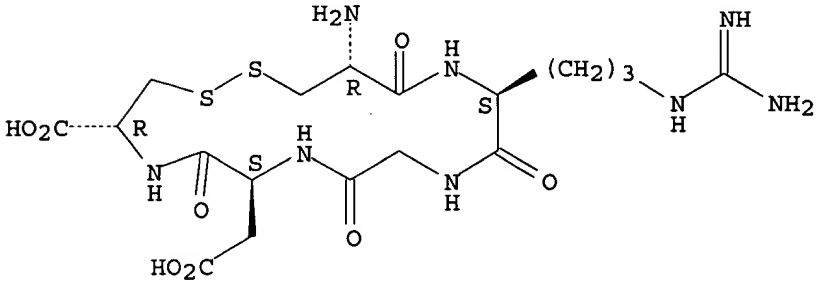
DETD . . . integrin composed of human α.sub.5 and β.sub.1, with a IC.sub.50 of 6 μM; it was 7-fold more potent than the * **CRGDC*** [SEQ ID NO: _____] (FIG. 11) or *CRRETAWAC* [SEQ ID NO: _____] peptides. Similar results were obtained with MG 63. . . disulfide bond-containing ACDCRGDCFCG [SEQ ID NO: _____] peptide had a significantly decreased activity toward α.sub.5β.sub.1 as compared to the smaller ***CRGDC*** [SEQ ID NO: _____] peptide and was only slightly better than the linear GRGDSP [SEQ ID NO: _____] peptide. We. . .

DETD . . . the peptide inhibited at IC.sub.50 of 0.6 μM and had a 40-fold higher affinity than the single disulfide bond-containing peptides ***CRGDC*** [SEQ ID NO: _____] and A*CRGDGWC*G [SEQ ID NO: _____]. Similar results were obtained with UCLA-P3 cells, where ACDCRGDCFCG [SEQ ID NO: _____] (IC.sub.50=0.6 μM) showed a 20-fold enhancement in activity relative to ***CRGDC*** [SEQ ID NO: _____]. Dimethyl sulfoxide at the concentrations corresponding to those added with the peptide had no effect on. . .

DETD . . . IC.sub.50 of 0.2 μM, the peptide was a 20-fold more effective inhibitor of attachment of IMR-90 cells to vitronectin than * **CRGDC*** [SEQ ID NO: _____] (FIG. 13). The RLD-containing cyclic peptide A*CPSRLDSPC*G [SEQ ID NO: _____] showed inhibitory activity

only at. . .
IT 91037-75-1 99896-85-2D, N- and C-terminal extension analogs
111119-28-9 129136-70-5D, N- and C-terminal extension analogs
135702-31-7 149635-29-0D, analogs 149635-34-7 152880-66-5
162901-68-0 167820-96-4D, analogs 167820-97-5D, analogs
167820-98-6D, analogs 167820-99-7D, analogs 167821-01-4D, analogs
167821-02-5D, analogs 168179-90-6D, N- and C-terminal extension analogs
168179-92-8 168179-93-9 168179-94-0 168179-95-1 168179-96-2
168179-97-3 168179-98-4 168179-99-5 168180-00-5D, analogs
168180-01-6D, analogs
(integrin binding properties of; novel integrin-binding peptides and their anal. and therapeutic uses in control of cellular adhesion)
IT **135702-31-7**
(integrin binding properties of; novel integrin-binding peptides and their anal. and therapeutic uses in control of cellular adhesion)
RN 135702-31-7 USPATFULL
CN L-Cysteine, L-cysteinyl-L-arginylglycyl-L-α-aspartyl-, cyclic (1→5)-disulfide (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L143 ANSWER 4 OF 8 USPATFULL on STN
AN 2002:167866 USPATFULL
TI Acoustically active drug delivery systems
IN Unger, Evan C., Tucson, AZ, United States
PA Bristol-Myers Squibb Medical Imaging, Inc., Princeton, NJ, United States (U.S. corporation)
PI US 6416740 B1 20020709
AI US 1998-75343 19980511 (9)
PRAI US 1997-46379P 19970513 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Dudash, Diana; Assistant Examiner: Sharareh, Shahnam
LREP Woodcock Washburn LLP
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN 9 Drawing Figure(s); 9 Drawing Page(s)
LN.CNT 5660
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed to targeted therapeutic delivery systems comprising a gas or gaseous precursor filled microsphere wherein said gas or gaseous precursor filled microsphere comprises an oil, a surfactant, and a therapeutic compound. Methods of preparing the targeted therapeutic delivery systems are also embodied by the present invention which comprise processing a solution comprising an oil and a surfactant in the presence of a gaseous precursor, at a temperature below the gel to liquid crystalline phase transition temperature of the surfactant to form gas or gaseous precursor filled microsphere, and adding to said microspheres a therapeutic compound resulting in a targeted therapeutic delivery system, wherein said processing is

selected from the group consisting of controlled agitation, controlled drying, and a combination thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . al. discloses a composition with a hydrophilic polymer outer coat and a hydrophobic core polymer, the two layers linked by **polyethylene glycol.**

DETD . . . may be an aqueous liquid or an organic liquid, for example. In addition, the resuspending medium may be a cryopreservative. **Polyethylene glycol**, sucrose, glucose, fructose, mannose, trebalose, glycerol, propylene glycol, and sodium chloride may be useful as resuspending medium.

DETD . . . optionally be included in AALs from the same reference include capmul MCM, Myverol 18-92, Cremophor EL, Centrophase 31, derivatives of **polyoxyethylene**, and those disclosed in U.S. Pat. No. 5,573,781 of Brown, the disclosures of which are hereby incorporated herein by reference. . .

DETD . . . methylcellulose, and methoxycellulose. Exemplary synthetic polymers suitable for use in the present invention include polyphosphazenes, polyethylenes (such as, for example, **polyethylene glycol** (including, for example, the class of compounds referred to as Pluronics®, which are generically known as poloxamers and are commercially available from BASF, Parsippany, N.J.), **polyoxyethylene**, and polyethylene terephthlate), polypropylenes (such as, for example, polypropylene glycol), polyurethanes (such as, for example, polyvinyl alcohol (PVA), polyvinyl chloride. . . ethyl acrylate, methyl methacrylate, 2-hydroxyethyl methacrylate (HEMA), lactic acid, glycolic acid, ε-caprolactone, acrolein, cyanoacrylate, bisphenol A, epichlorhydrin, hydroxyalkyl-acrylates, siloxane, dimethylsiloxane, **ethylene oxide**, **ethylene glycol**, hydroxyalkyl-methacrylates, N-substituted acrylamides, N-substituted methacrylamides, N-vinyl-2-pyrrolidone, 2,4-pentadiene-1-ol, vinyl acetate, acrylonitrile, styrene, p-amino-styrene, p-amino-benzyl-styrene, sodium styrene sulfonate, sodium 2-sulfoxyethyl-methacrylate, vinyl pyridine, aminoethyl methacrylates, 2-methacryloyloxy-trimethylammonium chloride, and polyvinylidene, as well polyfunctional crosslinking monomers such as N,N'-methylenebisacrylamide, **ethylene glycol** dimethacrylates, 2,2'-(p-phenylenedioxy)-diethyl dimethacrylate, divinylbenzene, triallylamine, polylactidecoglycolide, polyethylene-polypropyleneglycol, and methylenebis-(4-phenylisocyanate), including combinations thereof. Preferable polymers include polyacrylic acid, polyetyleneimine, polymethacrylic acid, polymethylmethacrylate, polysiloxane, polydimethylsiloxane, polylactic acid, **poly**(. **epsilon.-caprolactone**), epoxy resin, **poly**(**ethylene oxide**), **poly**(**ethylene glycol**), and polyamide (nylon) polymers. Preferable copolymers include the following: polyvinylidene-polyacrylonitrile, polyvinylidene-polyacrylonitrile-polymethylmethacrylate, polystyrene-polyacrylonitrile and poly d-1, lactide co-glycolide polymers. A preferred. . .

DETD . . . Exemplary semi-synthetic polymers include carboxymethylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, methylcellulose, and methoxycellulose. Exemplary synthetic polymers include polyphosphazenes, polyethylenes (such as, for example, **polyethylene glycol** (including the class of compounds referred to as Pluronics®, commercially available from BASF, Parsippany, N.J.), **polyoxyethylene**, and polyethylene terephthlate), polypropylenes (such as, for example, polypropylene glycol), polyurethanes (such as, for example, polyvinyl alcohol (PVA), polyvinyl chloride. . .

DETD . . . molecular weight of from about 400 to about 100,000. Suitable hydrophilic polymers are preferably selected from the group consisting

of **polyethylene glycol** (**PEG**), polypropylene glycol, polyvinylalcohol, and polyvinylpyrrolidone and copolymers thereof, with **PEG** polymers being preferred. Preferably, the **PEG** polymer has a molecular weight of from about 1000 to about 7500, with molecular weights of from about 2000 to about 5000 being more preferred. The **PEG** or other polymer may be bound to the lipid, for example, DPPE, through a covalent bond, such as an amide, carbamate or amine linkage. In addition, the **PEG** or other polymer may be linked to a targeting ligand, or other phospholipids, with a covalent bond including, for example, amide, ester, ether, thioester, thioamide or disulfide bonds. Where the hydrophilic polymer is **PEG**, a lipid bearing such a polymer will be said to be "pegylated." In preferred form, the lipid bearing a hydrophilic polymer may be DPPE-**PEG**, including, for example, DPPE-PEG5000, which refers to DPPE having a **polyethylene glycol** polymer of a mean weight average molecular weight of about 5000 attached thereto (DPPE-PEG5000). Another suitable pegylated lipid is distearoylphosphatidylethanolamine-**polyethylene glycol** 5000 (DSPE-PEG5000).

DETD . . . charged. Consequently, DPPA, which is negatively charged, may be added to enhance stabilization in accordance with the mechanism described above. DPPE-**PEG** provides a pegylated material bound to the lipid membrane or skin of the vesicle by the DPPE moiety, with the **PEG** moiety free to surround the vesicle membrane or skin, and thereby form a physical barrier to various enzymatic and other endogenous agents in the body whose function is to degrade such foreign materials. The DPPE-**PEG** may provide more vesicles of a smaller size which are safe and stable to pressure when combined with other lipids,. . . function as diagnostic imaging contrast media. A wide variety of targeting ligands may be attached to the free ends of **PEG.** The **PEG** typically functions as a spacer and improves targeting.

DETD . . . and di-glycerides, mono-ethanolamine, oleic acid, oleyl alcohol, poloxamer, for example, poloxamer 188, poloxamer 184, poloxamer 181, Pluronics® (BASF, Parsippany, N.J.), **polyoxyethylene** 50 stearate, polyoxyl 35 castor oil, polyoxyl 10 oleyl ether, polyoxyl 20 cetostearyl ether, polyoxyl 40 stearate, polysorbate 20, polysorbate. . . sodium 12, carrageenan, cellulose, dextran, gelatin, guar gum, locust bean gum, veegum, hydroxyethyl cellulose, hydroxypropyl methylcellulose, magnesium-aluminum-silicate, Zeolites®, methylcellulose, pectin, **polyethylene oxide**, povidone, propylene glycol alginate, silicon dioxide, sodium alginate, tragacanth, xanthan gum, α-d-gluconolactone, glycerol and mannitol; (iv) synthetic suspending agents, such as **polyethylene glycol** (**PEG**), polyvinylpyrrolidone (PVP), polyvinylalcohol (PVA), polypropylene glycol (PPG), and polysorbate; and (v) tonicity raising agents which stabilize and add tonicity, including,. . .

DETD . . . 5,149,543 which is incorporated herein by reference. In addition, nonionic surfactants selected from the group consisting of Triton-X® (octoxynols), Tweens® (**polyoxyethylene** sorbitans), Brij® (**polyoxyethylene** ethers), Pluronics® (**polyethylene glycol**), Zonyls® (fluorosurfactants), and Fluorads® may be useful in the present invention.

DETD . . . for example, ZONYL® surfactants identified as Telomer B, including Telomer B surfactants which are pegylated (i.e., have at least one **polyethylene glycol** group attached thereto), also known as **PEG**-Telomer B, available from the DuPont Company.

DETD . . . acid (DSPA); palmitic acid; stearic acid; arachidonic acid; oleic acid; lipids bearing polymers, such as chitin, hyaluronic acid, polyvinylpyrrolidone or **polyethylene glycol** (

PEG), also referred to herein as "pegylated lipids" with preferred lipid bearing polymers including DPPE-**PEG** (DPPE-**PEG**), which refers to the lipid DPPE having a **PEG** polymer attached thereto, including, for example, DPPE-PEG5000, which refers to DPPE having attached thereto a **PEG** polymer having a mean average molecular weight of about 5000; lipids bearing sulfonated mono-, di-, oligo- or polysaccharides; cholesterol, cholesterol. . . chain of about 6 carbons and another acyl chain of about 12 carbons; ceramides; non-ionic liposomes including niosomes such as **polyoxyethylene** fatty acid esters, **polyoxyethylene** fatty alcohols, **polyoxyethylene** fatty alcohol ethers, polyoxyalkylene sorbitan fatty acid esters (such as, for example, the class of compounds referred to as TWEEN.TM., commercially available from ICI Americas, Inc., Wilmington, Del.), including polyoxyethylated sorbitan fatty acid esters, glycerol **polyethylene glycol** oxystearate, glycerol **polyethylene glycol** ricinoleate, ethoxylated soybean sterols, ethoxylated castor oil, **polyoxyethylene**-polyoxypropylene polymers, and **polyoxyethylene** fatty acid stearates; sterol aliphatic acid esters including cholesterol sulfate, cholesterol butyrate, cholesterol isobutyrate, cholesterol palmitate, cholesterol stearate, lanosterol acetate,. . .

DETD . . . amides of phosphatidyl ethanolamine such as anandamides and methanandamides, phosphatidyl serine, phosphatidyl inositol and fatty acid esters thereof, cardiolipin, phosphatidyl **ethylene glycol**, acidic lysolipids, sulfolipids, and sulfatides, free fatty acids, both saturated and unsaturated, and negatively charged derivatives thereof. Phosphatidic acid and. . .

DETD . . . salts, and ZONYL® surfactants identified as Telomer B, including Telomer B surfactants which are pegylated (i.e., have at least one **polyethylene glycol** group attached thereto), also known as **PEG**-Telomer B, may be used to stabilize the lipid and/or vesicle compositions, and to act, for example, as a coating for. . .

DETD . . . also be employed. One or more emulsifying agents may also be incorporated into the oil, such as phospholipid, fatty acids, **polyethylene glycol** or other surfactants such as pluronic, Tween, Zonyl, and the like, to aid in preparation of a homogeneous suspension of. . .

DETD With respect to **polyethylene glycol** containing fragments, the following can be used, for example, PEG2-NHS ester, NHS-**PEG**-VS, NHS-**PEG**-MAL, methoxy-**PEG** -vinylsulfone, **PEG**-(VS).sub.2, methoxy-**PEG**-ald, **PEG**-(ald).sub.2, methoxy-**PEG**-epx, **PEG** -(epx).sub.2, methoxy-**PEG**-Tres, **PEG**-(Tres).sub.2, methoxy-**PEG**-NPC, **PEG**-(NPC).sub.2, methoxy-**PEG**-CDI, **PEG**-(CDI).sub.2, mPEG-Gly-OSu, mPEG-NLe-OSu, methoxy-SPA-**PEG**, (SPA).sub.2-**PEG**, methoxy-SS-**PEG**, (SS).sub.2-**PEG** all of which are available from Shearwater Polymers, Inc. (Huntsville, Ala.). Where these types of fragments are used, i.e., where. . .

DETD . . . fusion or agglutination from occurring. Additives which may be useful include sorbitol, mannitol, sodium chloride, glucose, dextrose, trehalose, polyvinyl-pyrrolidone and **poly(ethylene glycol)** (**PEG**), for example, **PEG** 400. These and other additives are described in the literature, such as in the U.S. Pharmacopeia, USP XXII, NF XVII,. . .

DETD . . . skilled in the art, including, for example, glycerol, propylene glycol; isopropyl myristate; urea in propylene glycol, ethanol and water; and **polyethylene glycol** (**PEG**).

DETD . . . 1 mg per ml of 82 mole percent dipalmitoylphosphatidylcholine (DPPC), 10 mole percent dipalmitoylphosphatidic acid (DPPA) and 8 mole percent dipalmitoylphosphatidylethanolarine-**polyethyleneglycol**

(DPPE-PEG5,000). All of the lipids were purchased from Avanti Polar Lipids, Alabaster, Ala. The liquid was sealed in an 2. . .

DETD The linear peptide **CRGDC** was synthesized by standard solid phase methodology using alpha amino-FMOC protection. This procedure will involve the use of the fluorenylmethoxycarbonyl. . . 2+2 minute washes of CH.sub.2Cl.sub.2. The remaining protected amino acids will be coupled in the same manner to provide the **CRGDC**-resin complex. Following binding of the FMOC-Val to the resin, further couplings will be initiated as set forth below.

DETD The peptide **CRGDC** requires only the sidechain protection of the lysines. A number of protecting group schemes are compatible with the synthetic scheme.. . . example, Boc-Lys with a fluorenylmethoxycarbonyl (FMOC) sidechain protecting group may be used to prevent the reaction of other amino acids, **PEG**, or the DPGS with the side chain group. In addition, a Boc-Asp with a β-carboxyfluorenylmethyl (OFm) ester bond may be used to protect the sidechain carboxyl. Prior to removal of the DPGS-**PEG**-**CRGDC** from the resin, mild conditions as 20% piperidine and N-methylpyrollidone can be initiated to remove both the FMOC group from. . .

DETD . . . the sidechain groups using 2% hydrazine in NMP, DMF, or CH.sub.2Cl.sub.2 for one hour. After removal of the sidechains, the DPGS-**PEG**-**CRGDC** will be washed with 2+2 min. NMP.

DETD . . . antiinflammatory drug. Dexarnethasone is soluble at 100 mg/L in water. A mixture is created by adding 80 mg of a **PEG** Telomer B (DuPont, Wilmington, Del.) to 20 mg of dexamethasone. The mixture is dissolved in methanol and rotary evaporated under. . . in methanol at 237 nm peak absorbance. The standard curve is between 2.5 and 25 μg/ml. The fractions that contained **PEG** Telomer B were suspensions and may not be scanned accurately. The remaining fractions are scanned and presumably contained the free,. . . of a 10 mg/ml reconstituted solution, dissolved in methanol and measured at UV 235 nm, demonstrates that 20% of the **PEG**-Telomer B aggregate complex is dexamethasone. The experiment showed the high payload efficiency of the fluorosurfactant aggregation technique.

DETD The lyophilized material comprising dexamethasone plus fluorosurfactant (20 mgs of **PEG** Telomer B) from Example 1 is suspended in 1.5 mls of soybean oil in a Teflon coated stoppered vial. To. . .

DETD . . . of compounds extracted from tissue. 320 μl of this solution was added to 1.5 ml of dipalmitoylphosphatidylcholine dipalmitoylphosphatidylethanolamine coupled to **polyethylene glycol** 5000, and dipalmitoylphosphatidic acid, in a ratio of about 82%:8%:10% (mole %) and the gas perfluoropropane in a 2 ml. . .

DETD . . . after IV injection of a bolus of different formulations of AALs. A comparison injection with imaging was also performed with DPPC:DPPE-**PEG**:DPPA (82%:8%:10% (mole %)) perfluorobutane gas filled contrast agent. Formulations of AALs which were tested included vesicles with two different concentrations. . . image heart and kidney. Images were recorded on videotape. The AALs gave less robust contrast than an equivalent dose of DPPC:DPPE-**PEG**:DPPA (82%:8%:10% (mole %)) perfluorobutane gas filed contrast agent but the duration of contrast was almost the same. Contrast could be. . .

CLM What is claimed is:

. . . from the group consisting of dioleoylphosphatidylcholine dimyistoylphosphatidylcholine, dipalmitoylphosphatidylcholine, and distearoyl-phosphatidylcholine; said phosphatidylethanolamine is selected from the group consisting of dipalmitoylphosphatidylethanolamin e, dipalmitoylphosphatidylethanolamine-**PEG** 5,000, dioleoyl-phosphatidylethanolamine, and N-succinyl-dioleoyl-phosphatidylethanolamine; and said phosphatidic acid is dipalmatoylphosphatidic acid; (ii) monitoring the targeted therapeutic delivery system using diagnostic. . .

. . . soybean oil, said microspheres comprise 82 mol percent dipalmitoylphosphatidyl choline, 10 mol percent dipalmitoylphosphatidic acid, and 8 mol percent dipalmitoylphosphatidyl ethanolamine-**polyethylene glycol** 5000, and said gaseous precursor is perfluorobutane.

. . . soybean oil, said microspheres comprise 82 mol percent dipalmitoylphosphatidyl choline, 10 mol percent dipalmitoylphosphatidic acid, and 8 mol percent dipalmitoylphosphatidyl ethanolamine-**polyethylene glycol** 5000, and said gaseous precursor is perfluorobutane.

. . . oil is soybean oil, said microspheres comprise 82 mol percent dipalmitoylphosphatidyl choline, 10 mol percent dipalmitoylphosphatidic acid, 8 mol percent dipalmitoylphosphatidylethanolamine-**polyethylene glycol** 5000 and apoloxamer, and said gaseous precursor is perfluorobutane.

. . . oil is soybean oil, said microspheres comprise 82 mol percent dipalmitoylphosphatidyl choline, 10 mol percent dipalmitoylphosphatidic acid, 8 mol percent dipalmitoylphosphatidylethanolamine-**polyethylene glycol** 5000 and a poloxamer, and said gaseous precursor is perfluorobutane.

. . . is soybean oil, said micropheres comprises 82 mol percent dipalmitoylphosphatidyl choline, 10 mol percent dipalmitoylphosphatidic acid, 8 mol percent dipalmitoylphosphatidyl ethanolamine-**polyethylene glycol** 5000 and a poloxamner, and said gaseous precursor is perfluorobutane.

. . . therapeutic compound is a dye, said oil is soybean oil, said micropheres comprises 82 mol percent dipalmitoylphosphatidylcholine, 8 mol percent dipalmitoylphosphatidylethanolamine-**polyethylene glycol** 5000, and 10 mol percent dipalmitoylphosphatidic acid, and said gaseous precursor is perfluoropropane.

. . . method of claim 1 wherein said therapeutic compound is dexamethasone, said micropheres comprises 82 mol percent dipalmitoylphosphatidylcholine , 8 mol percent dipalmitoylphosphatidylethanolamine-**polyethylene glycol** 5000, and 10 mol percent dipalmitoylphosphatidic acid, and said gas is perfluorobutane and nitrogen.

. . . method of claim 1 wherein said therapeutic compound is amphotericin, said micropheres comprises 82 mol percent dipalmitoylphosphatidylcholine , 8 mol percent dipalmitoylphosphatidylethanolamine-**polyethylene glycol** 5000, and 10 mol percent dipalmitoylphosphatidic acid, and said gas is selected from the group consisting of perfluorobutane and nitrogen.

. . .

IT **Polyoxyalkylenes, biological studies**
(ethers; preparation of solid porous matrixes for pharmaceutical uses)

IT **Polyoxyalkylenes, biological studies**
(preparation of solid porous matrixes for pharmaceutical uses)

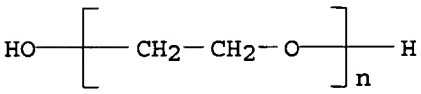
IT 646-04-8, trans-2-Pentene 661-54-1, Propyne-3,3,3-trifluoro 661-97-2 677-56-5, Propane-1,1,1,2,2,3-hexafluoro 678-26-2, Perfluoropentane 684-16-2, Hexafluoroacetone 685-63-2, Hexafluoro-1,3-butadiene 689-97-4, Vinyl acetylene 692-50-2, Hexafluoro-2-butyne 752-61-4, Digitalin 768-94-5, Amantadine 818-92-8, 3-FluoroPropylene 846-50-4, Temazepam 921-13-1, Chlorodinitromethane 927-84-4, Trifluoromethyl peroxide 928-45-0, Butyl nitrate 968-93-4, Testolactone 987-24-6, Betamethasone acetate 990-73-8, Fentanyl citrate 1070-11-7, Ethambutol hydrochloride 1119-94-4, Lauryltrimethylammonium bromide 1119-97-7, Myristyltrimethylammonium

bromide 1172-18-5 1177-87-3, Dexamethasone acetate 1191-96-4, EthylCyclopropane 1306-06-5, Hydroxylapatite 1397-89-3, Amphotericin B 1400-61-9, Nystatin 1404-04-2, Neomycin 1405-37-4, Capreomycin sulfate 1493-03-4, Difluoroiodomethane 1597-82-6, Paramethasone acetate 1630-94-0, 1,1-DimethylCyclopropane 1691-13-0, 1,2-Difluoroethylene 1722-62-9, Mepivacaine hydrochloride 1759-88-2 1867-66-9, Ketamine hydrochloride 2022-85-7, Flucytosine 2068-78-2, Vincristine sulfate 2314-97-8, IodotriFluoromethane 2366-52-1, 1-Fluorobutane 2375-03-3, Methylprednisolone sodium succinate 2392-39-4, Dexamethasone sodium phosphate 2511-95-7, 1,2-DimethylCyclopropane 2551-62-4, Sulfur hexafluoride 3116-76-5, Dicloxacillin 3385-03-3, Flunisolide 3458-28-4, Mannose 3485-14-1, Cyclacillin 3511-16-8, Hetacillin 3529-04-2, Benzyldimethylhexadecylammonium bromide 3810-74-0, Streptomycin sulfate 3858-89-7, Chloroprocaine hydrochloride 4185-80-2, Methotrimeprazine hydrochloride 4428-95-9, Foscarnet 4431-00-9, Aurintricarboxylic acid 4697-36-3, Carbenicillin 4786-20-3, Crotononitrile 4901-75-1, 3-Ethyl-3-methyldiaziridine 5534-09-8, Beclomethasone dipropionate 5536-17-4, Arabinosyl adenine 5611-51-8, Triamcinolone hexacetonide 5714-22-7, Sulfur fluoride (S2F10) 6000-74-4, Hydrocortisone sodium phosphate 7281-04-1, Benzyldimethyldodecylammonium bromide 7297-25-8, Erythritol tetranitrate 7439-89-6, Iron, biological studies 7440-01-9, Neon, biological studies 7440-06-4D, Platinum, compds., biological studies 7440-15-5, Rhenium, biological studies 7440-24-6, Strontium, biological studies 7440-26-8, Technetium, biological studies 7440-48-4, Cobalt, biological studies 7440-63-3, Xenon, biological studies 7440-65-5, Yttrium, biological studies 7601-55-0, Metocurine iodide 7637-07-2, biological studies 7647-14-5, Sodium chloride, biological studies 7681-14-3, Prednisolone tebutate 7727-37-9, Nitrogen, biological studies 7728-73-6 7782-41-4, Fluorine, biological studies 7782-44-7, Oxygen, biological studies 7783-82-6, Tungsten hexafluoride 9001-75-6, Pepsin 9001-78-9, Alkaline phosphatase 9002-01-1, Streptokinase 9002-04-4, Thrombin 9002-60-2, Adrenocorticotropic hormone, biological studies 9002-61-3 9002-72-6, Growth hormone 9002-79-3, Melanocyte stimulating hormone 9002-89-5, Poly(vinyl alcohol) 9003-11-6 9003-39-8, PVP 9004-10-8, Insulin, biological studies 9004-34-6, Cellulose, biological studies 9004-54-0, Dextran, biological studies 9004-61-9, Hyaluronic acid 9004-67-5, Methyl Cellulose 9005-25-8, Starch, biological studies 9005-27-0, HETA-starch 9005-32-7, Alginic acid 9005-49-6, Heparin, biological studies 9005-64-5, Polyoxyethylene sorbitan monolaurate 9005-65-6, Polyoxyethylene sorbitan monooleate 9005-66-7, Polyoxyethylene sorbitan monopalmitate 9005-67-8, Polyoxyethylene sorbitan monostearate 9005-71-4, Polyoxyethylene sorbitan tristearate 9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies 9011-14-7, PMMA 9011-97-6, Cholecystokinin 9015-68-3, Asparaginase 9015-71-8, Corticotropin releasing factor 9036-19-5, Octoxynol 9039-53-6, Urokinase 9061-61-4, Nerve growth factor 10024-97-2, Nitrogen oxide (N2O), biological studies 11000-17-2, Vasopressin 11056-06-7, Bleomycin 11096-26-7, Erythropoietin 13264-41-0, Cetyldimethylethylammonium chloride 13292-46-1, Rifampin 13311-84-7, Flutamide 13647-35-3, Trilostane 15500-66-0, Pancuronium bromide 15663-27-1, Cisplatin 15686-71-2, Cephalexin 15687-27-1, Ibuprofen 16009-13-5, Hemin 16136-85-9 17598-65-1, Deslanoside 18010-40-7, Bupivacaine hydrochloride 18323-44-9, Clindamycin 18378-89-7, Plicamycin 18773-88-1, Benzyldimethyltetradecylammonium bromide 20187-55-7, Bendazac 20274-91-3 20830-75-5, Digoxin 21829-25-4, Nifedipine 22204-53-1, Naproxen 22494-42-4, Diflunisal 22916-47-8, Miconazole 23110-15-8, Fumagillin 23541-50-6, Daunorubicin hydrochloride 24356-66-9 24764-97-4, 2-Bromobutyraldehyde 24991-23-9 25104-18-1, Polylysine 25151-81-9, Prostanoic acid 25316-40-9, Adriamycin **25322-68-3 25322-68-3D**, PEG, ethers 25322-69-4, Polypropylene glycol 25513-46-6, Polyglutamic acid

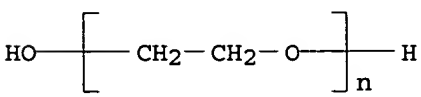
26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] 26100-51-6, Poly(lactic acid) 26171-23-3, Tolmetin 26780-50-7, Glycolide-lactide copolymer 26787-78-0, Amoxicillin 26839-75-8, Timolol 28911-01-5, Triazolam 29121-60-6, Vaninolol 29767-20-2, Teniposide 30516-87-1, Azidothymidine 31637-97-5, Etofibrate 33069-62-4, Taxol 33125-97-2, Etomidate 33419-42-0, Etoposide 33507-63-0, Substance p 34077-87-7, DiChlorotrifluoroethane 34787-01-4, Ticarcillin 36322-90-4 36637-19-1, Etidocaine hydrochloride 36791-04-5, Ribavirin 38000-06-5, Polylysine 38194-50-2, Sulindac 38821-53-3, Cephradine 39391-18-9, Cyclooxygenase 41575-94-4, Carboplatin 42399-41-7, Diltiazem 47141-42-4, Levobunolol 50370-12-2, Cefadroxil 50402-72-7, Piperidine-2,3,6-trimethyl 50700-72-6, Vecuronium bromide 50972-17-3, Bacampicillin 51264-14-3, Amsacrine 52205-73-9, Estramustine phosphate sodium 52365-63-6, Dipivefrin 53045-71-9, 1-Pentene-3-bromo 53188-07-1, Trolox 53678-77-6, Muramyldipeptide 53994-73-3, Cefaclor 54965-24-1, Tamoxifen citrate 55142-85-3, Ticlopidine 57223-18-4, 1-Nonen-3-yne 59277-89-3, Acyclovir 59467-96-8, Midazolam hydrochloride 60118-07-2, Endorphin 62031-54-3, Fibroblast growth factor 62229-50-9, Epidermal growth factor 62232-46-6, Bifemelane hydrochloride 62571-86-2, Captopril 62683-29-8, Colony stimulating factor 63659-18-7, Betaxolol 65277-42-1, Ketoconazole 68302-57-8 68367-52-2, Sorbinil 69279-90-9, Ansamitocin 72702-95-5, Ponalrestat 73218-79-8, Apraclonidine hydrochloride 73984-11-9 74381-53-6, Leuprolide acetate 74790-08-2, Spiroplatin 75847-73-3, Enalapril 76547-98-3, Lisinopril 77181-69-2, Sorivudine 80755-87-9 81486-22-8, Nipradilol 82159-09-9, Epalrestat 82410-32-0, Ganciclovir 82964-04-3, Tolrestat 83869-56-1, Granulocyte macrophage colony stimulating factor 86090-08-6, Angiostatin 88096-12-2 89149-10-0, 15-Deoxyspergualin 98023-09-7 99896-85-2 106956-32-5, Oncostatin M 113852-37-2, Cidofovir 116632-15-6, 1.2.3-Nonadecanetricarboxylic acid 2-hydroxytrimethylester 119813-10-4, Carzelesin 120279-96-1, Dorzolamide 120287-85-6D, Cetrorelix, derivs. 121181-53-1, Filgrastim 124389-07-7, Muramyltripeptide 127464-60-2, Vascular endothelial growth factor
(preparation of solid porous matrixes for pharmaceutical uses)

IT **25322-68-3 25322-68-3D**, PEG, ethers
(preparation of solid porous matrixes for pharmaceutical uses)

RN 25322-68-3 USPATFULL
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



RN 25322-68-3 USPATFULL
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



L143 ANSWER 5 OF 8 USPATFULL on STN
AN 2002:78245 USPATFULL
TI Novel targeted delivery systems for bioactive agents
IN Unger, Evan C., Tucson, AZ, UNITED STATES

Matsunaga, Terry Onichi, Tucson, AZ, UNITED STATES
Ramaswami, Varadarajan, Tucson, AZ, UNITED STATES
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PI US 2002041898 A1 20020411
AI US 2001-912609 A1 20010725 (9)
RLI Continuation-in-part of Ser. No. US 2000-703474, filed on 31 Oct 2000, PENDING Continuation-in-part of Ser. No. US 2000-478124, filed on 5 Jan 2000, PENDING
DT Utility
FS APPLICATION
LREP David A. Cherry, Esq., WOODCOCK WASHBURN KURTZ, MACKIEWICZ & NORRIS LLP, One Liberty Place - 46th Floor, Philadelphia, PA, 19103
CLMN Number of Claims: 100
ECL Exemplary Claim: 1
DRWN 5 Drawing Page(s)
LN.CNT 3658
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel targeted delivery systems for bioactive agents. In preferred form, the delivery systems comprise, in combination with an effective amount of a bioactive agent, a targeted matrix comprising a polymer and a targeting ligand. Preferably, the targeting ligand is covalently associated with the polymer and the bioactive agent is associated non-covalently with the polymer. Also in preferred embodiments, the bioactive agent is substantially homogeneously dispersed throughout the matrix. The compositions are particularly suitable as delivery vehicles with bioactive agents that have limited water solubility.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . 5,059,699), amino acid esters (Mathew et al. (1992) J. Med. Chem. 3B:145-151) as well as covalent conjugates of paclitaxel and **polyethylene glycol** (U.S. Pat. No. 5,648,506 to Desai et al.; Liu et al. (1999) J. Polymer Sci., Part A--Polymer Chem. 37:3492-3503). For. . .

SUMM . . . In order to increase the circulatory lifetime and subsequent bioavailability of these and other ligands, complexation with materials such as **polyethylene glycol** has proved useful. Most previous derivatization of **polyethylene glycol** has involved covalent attachment of a drug or biomolecule with or without a spacer moiety. See, e.g., U.S. Pat. No. 5,919,455. **Polyethylene glycol** has also been used to modify lipids such as dipalmitoylphophatidyl ethanolamine for incorporation into a delivery vehicle such as a. . .

DRWD . . . formulating composition comprising a matrix of a phospholipid conjugated to a linear hydrophilic polymer, namely, dipalmitoylphosphatidylethanolamine (DPPE) linked in to **polyethylene glycol** 5000 (**PEG** 5000), in accordance with an embodiment of the present invention. In the figure, "T" represents targeting ligands bound to the free ends of certain of the **PEG** chains.

DRWD . . . of a composition, in which a bioactive agent can be formulated, which is a matrix of a highly branched, dendrimeric **PEG**, in accordance with an alternate embodiment of the present invention. In the figure, "T" represents targeting ligands bound to the free ends of certain of the **PEG** chains.

DRWD . . . schematic representation of a composition, in which a bioactive agent can be formulated, which is a matrix formed from star **PEG**, in accordance with another alternate embodiment of the present invention. In the figure, "T" represents targeting ligands bound to the free ends of certain of the **PEG** chains.

DRWD . . . a composition, in which a bioactive agent can be formulated, which is a matrix of a lower molecular weight, branched **PEG**, in accordance with still another alternate embodiment of the present invention. In the figure, "T" represents targeting ligands bound to the

free ends of certain of the **PEG** chains.

DRWD . . . polymer comprises a block copolymer with an inner more hydrophobic block, e.g. polylactide, and an outer less hydrophobic block, e.g. **polyethyleneglycol**. In the figure, "T" represents targeting ligands bound to the free ends of certain of the outer **PEG** arm chains.

DETD . . . herein, refers to a three dimensional structure which may comprise, for example, a single molecule of a polymer, such as **PEG** associated with one or more molecules of a bioactive agent, or a complex comprising a plurality of polymer molecules in. . .

DETD . . . relatively more hydrophilic or relatively more hydrophobic. Examples of suitable, relatively more hydrophilic polymers include, but are not limited to, **polyethylene glycol**, polypropylene glycol, branched polyethylene imine, polyvinyl pyrrolidone, polylactide, poly(lactide-co-glycolide), polysorbate, **polyethylene oxide**, **poly(ethylene oxide**-co-propylene oxide), poly(oxyethylated) glycerol, poly(oxyethylated) sorbitol, poly(oxyethylated glucose), polymethyloxazoline, polyethyloxazoline, polyhydroxyethyloxazoline, polyhydroxypropyloxazoline, polyvinyl alcohol, poly(hydroxyalkylcarboxylic acid), polyhydroxyethyl acrylic acid, polyhydroxypropyl methacrylic. . .

DETD . . . Examples of suitable, relatively more hydrophobic polymers include linear polypropylene imine, polyethylene sulfide, polypropylene sulfide, polyethylenesulfonate, polypropylenesulfonate, polyethylene sulfone, polyethylenesulfonylethyleneimine, **polycaprolactone**, polypropylene oxide, polyvinylmethylether, polyhydroxyethyl acrylate, polyhydroxypropyl methacrylate, polyphosphazene and derivatives, mixtures and copolymers thereof.

DETD [0059] Preferred among the foregoing polymers for use in the present compositions are **polyethylene glycol** (**PEG**), polypropylene glycol (PPG), and copolymers of **PEG** and PPG, or **PEG** and/or PPG containing some fraction of other monomer units (e.g., other alkylene oxide segments such as propylene oxide). Another particularly preferred copolymer is a branched polymer of **PEG** and PPG, particularly wherein the PPG units comprise the innermost portion of the structure and the **PEG** units comprise the outer portions of the arms of the branched structure. Also preferred among the foregoing polymers are polysorbates,. . .

DETD . . . hydrophilic block. In preferred embodiments, the inner block may comprise polypropylene oxide, polylactide or polylactide-coglycolide and the outer block comprises **polyethylene glycol**. Also in preferred embodiments, the targeting ligands may be attached to the outermost portion of the arms.

DETD . . . chemical interaction or association with the bioactive agent. For example, the drug irinotecan is a lipophilic cation, and the drug **camptothecin** is hydrophobic although the pyridine residue may be attached to the 10-hydroxy position of **camptothecin** to provide a pro-drug. The pyridine moiety may also carry a positive charge at physiological pH from the quaternary amine.. . . acids, for example, glutamate, into the polyleucine polypeptide, may serve to increase the interaction of the predominantly polyleucine polypeptide with **camptothecin**. In general, for bioactive agents such as irinotecan, which are lipophilic cations, incorporating an anionic segment into the polypeptide may. . .

DETD . . . however, the hydrophobic segment of amino acids may be covalently bound to another polymer, preferably a hydrophilic polymer, such as **polyethyleneglycol** (**PEG**). For example, a decapeptide of polyleucine may be attached to a hydrophilic polymer, such as **PEG**, for example, via the free amino end of the polyleucine peptide and the free carboxyl end of α-amino, γ-carboxy **PEG**. The free end of the **PEG**, via its amino group, may then be used to attach a targeting ligand, for

example, a peptide via its terminal carboxyl group. In such embodiments, the hydrophilic polymer, for example, **PEG**, may vary in length such that it's molecular weight may range, for example, from about 400 to about 100,000 daltons,. . . hydrophilic polymer in the context of the present embodiment, is about 3,500 daltons. Generally speaking, a hydrophilic polymer, such as **PEG**, having a higher molecular weight, may afford a longer circulation lifetime, but may decrease the affinity of the targeted matrix. . .

DETD . . . In so doing, a branching structure may be created which comprises a plurality of hydrophobic domains. Hydrophilic polymers, such as **PEG**, may then in turn be attached to the free ends of the pendant chains of hydrophobic amino acids to create a branched block polymer comprised of amino acids and **PEG**. When such a structure is created from a backbone and multiple chains, then the structure preferably has from about 3. . .

DETD . . . particularly preferred. Examples of lower molecular weight polymers include polymers such as TWEEN® 80 (about 1,200 daltons) or small branched **PEGs** on the order of from about 1000 to about 2000 daltons.

DETD . . . daltons, and still more preferably about 40,000 daltons. Preferably, each arm has the same unit size of polymer, such as **PEG**, e.g, about 5000 daltons each for an 8-armed **PEG**.

DETD . . . or blocks in each arm may vary. For example, with an 8 arm branched copolymer of polypropylene glycol (PPG) and **PEG**, when 50% is PPG and 50% is **PEG**, both the PPG segment and the **PEG** segment will have a molecular weight about 2500 daltons, with the **PEG** forming the outer portion of the arm.

DETD [0071] As stated above, a preferred polymer of the present invention is **polyethylene glycol** which may be either a branched **PEG** (including "dendrimeric" **PEG**, i.e., higher molecular weight, highly branched **PEG**) or star **PEG**. In certain embodiments, the polymer may be covalently associated with a lipid, such as a phospholipid moiety in which the. . . may tend to associate in an aqueous medium. This is depicted schematically in FIG. 1. Combinations of different types of **PEG** (e.g., branched **PEG** and linear **PEG**, star **PEG** and linear **PEG**, branched **PEG** and phospholipid-conjugated linear **PEG**, and the like) may also be employed.

DETD [0072] In embodiments involving branched **PEG**, the branched **PEG** may have a molecular weight of from about 1000 to about 600,000, preferably from about 2000 to about 100,000, more preferably from about 20,000 to about 40,000. Branched **PEG** is commercially available, such as from Nippon Oil and Fat (NOF Corporation, Tokyo, Japan) and from Shearwater Polymers (Huntsville, Ala.), or may be readily synthesized by polymerizing lower molecular weight linear **PEG** molecules (i.e., **PEG** 2000 or smaller) finctionalized at one or both termini with a reactive group. For example, branched **PEG** may be synthesized by solution polymerization of lower molecular weight **PEG** acrylates (i.e., **PEG** molecules in which a terminal hydroxyl group is replaced by an acrylate functionality, i.e., --O--(CO)--CH.dbd.CH.sub.2) in the presence of a free radical polymerization initiator such as 2,2'-azobisisobutyronitrile (AIBN). If desired, mixtures of **PEG** monoacrylates or monomethacrylates having different molecular weights may be used in order to synthesize a branched polymer having branches or arms of different lengths. Higher molecular weight, highly branched **PEG**, e.g. branched **PEG** having a molecular weight of greater than about 10,000 and at least about 1 arm (i.e., one branch point) per 5000 Daltons, may sometimes be referred to herein as dendrimeric **PEG**. Dendrimeric **PEG** may preferably be formed by reaction of a hydroxyl-substituted amine, such as triethanolamine, with lower molecular weight **PEG** that may be linear, branched or star, to form a molecular lattice that may serve as

the spatially stabilized matrix for delivery of an entrapped bioactive agent. Dendrimeric structures, including dendrimeric **PEG** are described, for example, in Liu et al. (1999) PSTT 2(10):393-401, the disclosure of which is hereby incorporated herein by reference, in its entirety. Embodiments involving compositions comprising highly branched, high molecular weight dendrimeric **PEG** and lower molecular weight branched **PEG** are schematically illustrated in FIGS. 2 and 4, respectively.

DETD [0073] Star molecules of **PEG** are available commercially (e.g., from Shearwater Polymers, Huntsville, Ala.) or may be readily synthesized using free radical polymerization techniques as. . . et al., U.S. Pat. No. 5,648,506, the disclosures of which are hereby incorporated herein by reference, in their entireties. Star **PEG** typically has a central core of divinyl benzene or glycerol. Preferred molecular weights for star molecules of **PEG** may be from about 1000 to about 500,000 Daltons, with molecular weights of about 10,000 to about 200,000 being preferred. A formulation of the invention which employs star **PEG** is schematically illustrated in FIG. 3. The bioactive agent may be associated with the branches and/or arms of the matrix,. . .

DETD . . . or conjugated to a lipid, preferably a phospholipid, to provide a polymer-lipid conjugate, as in the case, for example, of **PEG** -phospholipid conjugates (also referred to as "PEGylated" phospholipids). As with the polymers discussed above, the polymer in the polymer-lipid conjugates, such as **polyethylene glycol** , may be branched, star or linear. Generally speaking, the molecular weight of the polymer in the polymer-lipid conjugates may be. . . to about 40,000. It will be appreciated by those skilled in the art that in the case, for example, of **polyethylene glycol**, the aforementioned molecular weight ranges may correspond to a polymer containing about 20 to about 2000 **ethylene oxide** units, preferably about 20 to about 1000 **ethylene oxide** units.

DETD [0076] wherein R.sup.1 and R.sup.2 are the acyl groups, R.sup.3 represents the polymer, e.g., a polyalkylene oxide moiety such as **poly**(**ethylene oxide**) (i.e., **polyethylene glycol**), poly(propylene oxide), **poly**(**ethylene oxide**-co-propylene oxide) or the like (for linear **PEG**, R.sup.3 is --O--(CH.sub.2CH.sub.2O).sub.n--H), and L is an organic linking moiety such as a carbamate, an ester, or a diketone having. . .

DETD . . . and preferred saturated acyl moieties are palmitate, myristate and stearate. Particularly preferred phospholipids for conjugation to linear, branched or star **PEG** herein are dipalmitoylphosphatidylethanolamine (DPPE) and 1-palmitoyl-2-oleylphosphatidylethanolamine (POPE).

DETD . . . which are hereby incorporated herein by reference, in their entirety. For example, preparation of a polymer-lipid conjugate, such as a **PEG**-phospholipid conjugate, may be carried out by activating the polymer to prepare an activated derivative thereof, having a functional group suitable. . . alcohol, a phosphate group, a carboxylic acid, an amino group or the like. For example, a polyalkylene oxide such as **PEG** may be activated by the addition of a cyclic polyacid, particularly an anhydride such as succinic or glutaric anhydride (ultimately. . .

DETD . . . for negatively charged (e.g., anionic) bioactive agents. To insert such groups, a terminal hydroxyl group of a polymer such as **PEG** may be converted to a carboxylic acid or phosphate moiety by using a mild oxidizing agent such as chromic (VI). . .

DETD . . . to the polymer include, but are not limited to, the following. A terminal hydroxyl group of a polymer, for example, **PEG**, may be replaced by a thiol group using conventional means, e.g., by reacting a hydroxyl-containing polymer, such as **PEG** with a

sulfur-containing amino acid such as cysteine, using a protected and activated amino acid. The resulting polymer ("**PEG**-SH") is also commercially available, for example from Shearwater Polymers. Alternatively, a mono(lower alkoxy)-substituted polymer, such as monomethoxy **polyethylene glycol** (MPEG) may be used instead of a non-substituted polymer, e.g., **PEG**, so that the polymer terminates with a lower alkoxy substituent (such as a methoxy group) rather than with a hydroxyl group. Similarly, an amino substituted polymer, such as **PEG** amine, may be used in lieu of the corresponding non-substituted polymer, e.g., **PEG**, so that a terminal amine moiety (--NH.sub.2) may be present rather than a terminal hydroxyl group.

DETD . . . as in a copolymer wherein propylene oxide groups (--CH.sub.2CH.sub.2CH.sub.2O--) or polylactide or polylactide-coglycolide have been substituted for some fraction of **ethylene oxide** groups (--CH.sub.2CH.sub.2O--) in **polyethylene glycol.** Incorporating propylene oxide, polylactide, polylactide-coglycolide, or **polycaprolactone** groups may tend to increase the stability of the spatially stabilized matrix, thus decreasing the rate at which the bioactive. . .

DETD . . . an alcohol; acetal linkages may be synthesized by reaction of an aldehyde and an alcohol; and the like. Thus a **polyethylene glycol** matrix containing hydrolyzable linkages "X"

DETD -**PEG**-X-**PEG**-

DETD [0084] may be synthesized by reaction of -**PEG**-Y with -**PEG**-Z wherein Z and Y represent groups located at the terminus of individual **PEG** molecules and are capable of reacting with each other to form the hydrolyzable linkage X.

DETD . . . In such embodiments, the peptide, such as, for example, decaleucine, may be prepared and then a hydrophilic polymer, such as **PEG**, may be coupled to the free end of the homopolymer of amino acids and then, if desired, a targeting ligand may be prepared on the free end of the **PEG** to thereby create the conjugate polyLeu-**PEG**-targeting ligand. This conjugate may then be cleaved from the resin and the product isolated, for example, by chromatography. Another block of hydrophilic polymer, for example, **PEG**, may be coupled to the other terminus of the hydrophobic peptide using solution phase chemistry. Various blocks of the peptides. . .

DETD . . . agent-binding region. Recombinant techniques may also be used to produce peptides for isolation and coupling to other materials such as **PEG** for use in this invention. Variations in the synthetic techniques employed will be apparent to one skilled in the art. . .

DETD . . . number of free arms in the branched polymer molecule. For example, in the compositions of the present invention, a branched **PEG** molecule containing 4 arms may also preferably contain 4 covalently associated targeting ligands, preferably to provide one targeting molecule per arm of **PEG.** As the branching of the polymer employed increases, the number of targeting ligands associated with the polymer may increase also.. . .

DETD . . . useful as targeting agents in accordance with the present invention. These motifs include the amino acid sequences DGR, NGR, and **CRGDC.** These peptides are generally characterized by their ability to inhibit integrin-expressing cells from binding to extracellular matrix proteins, and in. . .

DETD . . . prostaglandin D2. For example, the free carboxylic acid group in iloprost may be covalently linked with a polymer, such as **PEG** , via an ester linkage. Modified **PEGs** may also react similarly with iloprost to form a thioester, carbamate, amide or ether linkage, depending on the modification of the **PEG** moiety, as will be appreciated by those of skill in the art, once armed with the teachings of the present. . .

DETD . . . the polymer when utilizing linker groups having two unique terminal functional groups. As discussed above, bifunctional polymers,

and especially bifunctional **PEGs**, may be synthesized using standard organic synthetic methodologies, and many of these materials are available commercially. More specifically, the polymers. . .

DETD . . . above. The activated amine groups can be used, in turn, to couple to a functionalized polymer, such as, for example, α-amino-ω-hydroxy- **PEG** in which the ω-hydroxy group has been protected with a carbonate group. After the reaction is completed, the carbonate group. . .

DETD [0138] Larger polypeptides and proteins may also be linked to reactive terminal groups of **PEG** by methods well-established in the art. Generally, the monomethoxy derivative of **PEG** is first activated by one of several methods using cyanuric chloride, carbonyl diimidazoles, phenylchloroformate or succinimidyl esters (Mehvar, R., J.. . .

DETD [0139] Those of skill in the art will note that the particular coupling method used to derivatize a particular **PEG** and a particular protein may depend on the relative sizes of the polymer and protein being used, with the ideal coupling ratio approximating a 1:1 molecular size between the **PEG** and the protein.

DETD . . . for the polymer than for aqueous media. For example, preferred bioactive agents include materials that have substantially greater solubility in **PEG** 400 than in water.

DETD [0153] anticancer agents, including antineoplastic agents--paclitaxel, docetaxel, **camptothecin** and its analogues and derivatives (e.g., 9-**aminocamptothecin**, 9-**nitrocamptothecin**, 10-hydroxy-**camptothecin**, irinotecan, topotecan, 20-O-glucopyranosyl **camptothecin**), taxanes (baccatins, cephalomannine and their derivatives), carboplatin, cisplatin, interferon-2A, interferon-2B, interferon-N3 and other agents of the interferon family, levamisole, altretamine,. . .

DETD [0174] topoimerase inhibitors--**camptothecin**, anthraquinones, anthracyclines, temiposide, etoposide, topotecan and irinotecan.

DETD . . . prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. A dispersion can also be prepared in glycerol, liquid **polyethylene glycols** and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to. . .

DETD . . . carrier may be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, liquid **polyethylene glycol** and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use. . .

DETD [0200] This example is directed to the preparation of the peptide **CRGDC.**

DETD . . . of 0.1% TFA followed by enrichment with acetonitrile. The purified peptide was isolated and dried by lyophilization to yield cyclic **CRGDC** in good yield.

DETD [0207] This example is directed to the preparation of phosphorylated **PEG.**

DETD [0208] Branched **PEG** (4-arms, 20 kD, Shearwater Polymers, Huntsville, Ala.) (0.529 g) was dissolved in 10 mL acetonitrile (EM Science, HPLC grade) in a 25 mL round bottomed flask. Twenty microliters of triethylamine (Sigma Chemical; 1.43+10.sup.-4 mol) was added into the **PEG**/acetonitrile solution. Five microliters of phosphorous oxychloride (POCl.sub.3) (Aldrich Chemical) was then added to 7 mL of acetonitrile in a side arm addition funnel and slowly allowed to drip into the stirred **PEG**/acetonitrile solution over 15 minutes. After 12-14 hrs of stirring at ambient temperature, the reaction mixture was quenched with 25 mL. . . P in the resulting white flaky powder indicated that one or two ends of the branches were phosphorylated. The phophorylated **PEG** 2000 was reacted with 1.5 equivalent of carbonyldiimidazole to from the mixed anhydride in the DCM. The precipitated carbonylimidazole was. . .

DETD [0209] This example was repeated using twice the amount of POCl.sub.3. In the subsequent analysis, approximately 30% of the **PEG** showed phosphorylation on all four arms. The resulting compound was separated from the incompletely phosphorylated **PEG** adducts via ion-exchange chromatography.

DETD [0217] This example is directed to the preparation of **CRGDC** -branched **PEG.**

DETD [0218] The preparation of **CRGDC** described in Example 1 is repeated followed by deprotection of the terminal Fmoc on the cysteine. After washing with DCM, MeOH, and DCM, the resin is then treated with three equivalents of DIC and one equivalent of phosphorylated branched **PEG** 2000 mixed anhydride from Example 2. The resin is reacted for four hours and coupling is tested for completion using. . .

DETD [0221] This example is directed to the preparation of **CRGDC** -Branched **PEG**-amine.

DETD [0222] Branched **PEG** (4 Arm, 20 K, Shearwater Corporation) is reacted with 4 equivalents of FMOC Glycine (American Peptide Company, Inc, Calif.), 1 equivalent of DIC and HOBT in DCM at room temperature for 4 hours. After deprotection, the product, HO-**PEG** -Glycine-NH.sub.2, is purified by standard chromatographic techniques, and is then reacted with the peptide **CRGDC** combining one equivalent of each reactant using the methodology of Example 4.

DETD [0224] This example is directed to the preparation of **CRGDC** -percarboxylated branched **PEG.**

DETD [0225] Branched **PEG** (4 Arm, 20 K, Shearwater Corporation) is reacted with 4 equivalents of chloroacetic acid and 8 equivalents of sodium hydroxide. . . reaction is quenched by addition of sodium dihydrigephosphate and adjusting the pH to 7.0, and the resulting product, percarboxylated branched **PEG**, is purified by dialysis. The percarboxylated branched **PEG** is then coupled with the **CRGDC** peptide using the same coupling, cyclization, and isolation procedures as described in Examples 1 and 3.

DETD [0227] This example is directed to the preparation of **PEG**-PPG copolymers with pentaerythritol cores.

DETD [0228] A. Branched block **PEG**-PPG copolymer with a pentaerythritol core.

DETD [0229] Pentaerythritol (1 equiv.; Aldrich, 99+%, FW 136.15) is reacted with 4 equivalents of FMOC-**PEG**-NHS (Shearwater Corporation, MW 3400) in the presence of DIC in DCM. The reaction is allowed to proceed for 4 hours. . .

DETD [0230] B. Branched PPG-**PEG** copolymer with a pentaerythritol core.

DETD . . . FMOC group is removed as described in Example 1, and the resulting material is then reacted with an excess of FMOC-**PEG** -NHS (Shearwater Corporation) (MW 3000) in the presence of DIC/HOBT to form the amide linkages. The reaction is carried out at. . .

DETD [0233] This example is directed to the preparation of **PEG** core with polylactide or polyglycolide arms.

DETD [0234] In preparation for synthesis, polyglycolide (DuPont) and DL-polylactide (Aldrich) are freshly recrystallized from ethyl acetate. **PEG** oligomers of various molecular weights (Fluka or Polysciences) are dried under vacuum at 110° C. prior to use. Acryloyl chloride. . .

DETD [0235] A. **PEG** with polyglycolide arms.

DETD [0236] A 250 ml round bottom flask is flame dried under repeated cycles of vacuum and dry argon. **PEG** (20 g; molecular weight 10,000), 150 mL of xylene and 10 micrograms of stannous octoate are charged into the flask. The flask is heated to 60° C. under argon to dissolve the **PEG**, and cooled to room temperature. Polyglycolide (1.16 g) is added to the flask and the reaction mixture is refluxed for 16 hr. The resulting copolymer (10 K **PEG**-polyglycolide) is separated on cooling, recovered by filtration, and used directly as is in subsequent reactions.

DETD [0237] B. **PEG** with polylactide arms.

DETD [0238] **PEG** (MW 20,000) is dried by dissolving in benzene and distilling off the water as benzene azeotrope. In a glove bag, 32.43 g of **PEG** 20 k, 2.335 g of DL-polylactide and 15 mg of stannous octoate are charged into a 100 mL round bottom. . .

DETD [0239] Branched **PEG** may also be used to synthesize the corresponding polylactide and polyglcolide adducts. In these cases, the 4.64 g of polyglycolide and 8.34 g of DL-polylactide are used as reactants, respectively, to the molar equivalent of branched **PEG** from the procedures described above.

DETD . . . The product has four equivalents of polyglycolide which are available for further derivatization, for example, with phosphorylated or percarboxylated branched **PEG.**

DETD . . . above reaction is repeated using DL-polylactide to generate the corresponding polylactide derivative which may also be further derivatized with branched **PEG.** The resulting complexes contain a central core of penterythritol, 4 arms of polyglycolide or polylactide and terminal units of 10 Kd branched **PEG.**

DETD . . . polymers of the present invention. The terminal cysteine allows use of a maleimide linker to bind the protein to branched **PEG.** By first activating branched **PEG** to contain maleimide groups, the FGF is linked to the branched **PEG** as a bioconjugate. The maleimide reacts specifically with the sulfhydryl group of the cysteine when the pH is kept between 6.5 and 7.5. The modified bFGF is mixed with the maleimide substituted branched **PEG** at pH 7. The mixture is incubated overnight at room temperature to allow the binding to occur. The bound material. . .

DETD [0257] 100 mg of a PEGylated phospholipid or branched **PEG**, 40 kD, Shearwater Polymers, Huntsville, Ala.) is dissolved in t-butanol (10 mL), and the resulting solution is heated over a. . . the solution clarifies. Tween 80 is added in a ratio from at least 1:5 to as much as 5:1 Tween 80:**PEG** component and sonication is applied again until the mixture clarifies. 10 mg of paclitaxel (Hauser Laboratories) is then added, followed. . .

DETD [0262] The following example is directed to the preparation of a targeted composition comprising **camptothecin** and a polymeric matrix comprising Tween (polysorbate).

DETD [0263] A. 1.68 g of branched **polyethylene glycol** (bPEG), MW 20,000, 4 branches (Shearwater Polymers, Huntsville, Ala.) was dissolved in 30 mL of t-butanol in a round bottom. . . stirrer for approximately 20 min until the bPEG dissolved. This resulted in a clear solution to which 8.90 mg of **camptothecin** (Natland International Corporation, NC) and 10 mL of dichloromethane was added and dissolved with slight heating and exposure to ultrasound. The solution acquired a slight yellow tint after the **camptothecin** dissolved. Another 20 mL of t-butanol was added to the solution. The flask was then immersed in liquid nitrogen (-78°. . . flaky powder that was then hydrated with 20 mL of water. Water for hydration contained 303.8 mg (1% wt/vl) of **polyoxyethylene**-sorbitan monooleate (Tween 80). The hydrated material was dispersed using a microfluidizer, Model 110, Microfluidics International Corp. (Newton, Mass.). The dispersion. . . pale-yellow tint, and showed no presence of crystals when inspected using a polarized light microscope. The final concentration of the **camptothecin** in this particular formulation was 0.3 mg/mL. The same technique could be employed to increase the concentration up to 5.0. . .

DETD [0265] A. Pentaerythritol (Aldrich, 99+%, FW 136.15; 1 equivalent) is reacted with 3 equivalents of FMOC-**PEG**-NHS (Shearwater Corporation, MW 3400) in the presence of dicyclohexylcarbdiimide in DCM. The reaction is allowed to proceed for 4 hours. . . water to remove other unreacted reagents. The homogeneity is checked using reverse phase HPLC, and the resulting product, with three **PEG** arms, is reacted with stearic acid succinimide in the presence of DIC and HOBT

for 4 hours in DCM. The. . .

DETD [0266] B. The procedure from Step A may be modified to include a central **PEG** with two fatty acid arms or peptide arms, which may also include further units of **PEG**-amine for additional derivatization. A method derived from that of Clochard, et al., Macromol. Rapid Comm. (2000) 21:853-859 may also be used, in which bifunctional **PEG**-amine (NH-**PEG**-NH) is flanked in two hydrolytically labile amide linkages by groups which can be either peptides or proteins. The reaction starts with aminoethyl-terminated **PEG** and cis-aconitic hydride.

DETD . . . activator (t-PA) as described in Delgado C.,et al., Crit.Rev Ther Drug Carrier Sys,(1992) 9:249-304. The terminal --OH groups of the **PEG** are first activated with 1,1'-carbonyldiimidazole before addition of the t-PA.

DETD . . . a protein with protected side chain amino groups, is an example of one of several means for coupling proteins to **PEG.** Harris, J. M., ed., "**Polyethylene Glycol** Chemistry. Biotechnical and Biomedical Applications," Plenum Press, 1992.

DETD [0271] This example is directed to the preparation of biodegradable branched **PEG** (3 Arm).

DETD [0272] **PEG**-2 Succinmide, MW 10,000 (Shearwater Corporation) is reacted with FMOC-aminoethyl ester of stearic acid in the presence of DIC and HOBT. . .

DETD [0274] Example 16 is repeated except methoxy **PEG** arms are substituted by FMOC-**PEG** by reacting FMOC-**PEG**-NHS ester with carboxy-protected lysine using techniques used for the synthesis of **PEG**-2 Succinimde.

DETD [0276] This example is directed to the preparation of N,N'-distearyldiaminobutryl-PEG3400-**CRGDC** (cyclic) using standard solid-phase techniques with Fmoc protecting groups.

DETD [0300] The final product from Example 18 is added to DPPE-**PEG** -5000 (Avanti Polar Lipids, Alabaster, Ala.) in a ratio of 9:1 mol/mol in t-butyl alcohol. Paclitaxel (10 mg) (Natural Pharmaceuticals, Boston,. . .

DETD [0302] This example is directed to the preparation of Methoxy-**PEG**-decaleucine or Methoxy-**PEG**-decaisoleucine using standard solid-phase techniques with Fmoc protecting groups.

DETD . . . the last amino acid is removed with the piperidine solution. The resin is dried to obtain a starting weight, and methoxy-**PEG** -succinimidyl propionate (mPEG-SPA; 1 equiv.), having a molecular weight of either 2000 or 5000, is added as a solid using sufficient. . . Additional HOBT (solid) and DIC (neat) is added at approximately 24 hrs. After draining the reaction mixture, while saving the **PEG** solution, the resin is washed and dried over N.sub.2. As 100% complete coupling is not achieved, the extent of coupling. . .

DETD [0315] B. Procedure (1) Preparation of Fmoc-**PEG**.sub.3400-VVVVV

DETD . . . Additional HOBT (solid) and DIC (neat) is added at approximately 24 hrs. After draining the reaction mixture, while saving the **PEG** solution, the resin is washed and dried over N.sub.2. As 100% complete coupling is not achieved, the extent of coupling. . .

DETD [0327] Fmoc-**PEG**-VVVVV-CO.sub.2NHS is coupled to Fmoc-KKKK-Wang using 12 equivalents with 12 equivalents each of 1 M HOBT/NMP and 1 M DIC/NMP. The. . .

DETD . . . is removed from the last valine with the piperidine solution. The resin is dried to obtain a starting weight, and methoxy-**PEG** -succinimidyl propionate (mPEG-SPA) (1 equiv.), having a molecular weight of 2000 or 5000, is added as a solid using sufficient NMP. . . Additional HOBT (solid) and DIC (neat) is added at approximately 24 hrs. After draining the reaction mixture, while saving the **PEG** solution, the resin is washed and dried over N.sub.2. As 100% complete coupling is not achieved, the extent of coupling. . .

DETD [0335] The resin is divided and a portion of which is set aside for later use. To cleave the Dde-K(methoxy-**PEG**-VVVVV) from the

resin, resin is added with stirring to a solution of 95% trifluoroacetic acid (TFA) in water (v/v). The. . .

DETD [0336] The Dde protecting groups are removed from the retained Dde-K(methoxy-**PEG**-VVVVV) using 2% hydzine in DMF. The reaction mixture is stirred at room temperature for 3 minutes, after which the resin. . .

DETD [0337] Dde-K(methoxy-**PEG**-VVVVV) is coupled to the deprotected K(methoxy-**PEG**-VVVVV) using 3 equivalents with 3 equivalents each of 1 M HOBT/NMP and 1 M DIC/NMP. Sufficient NMP is added to. . .

DETD [0340] This example is directed to the preparation of CRGDS-**PEG** -LLLLLLLLL using standard solid-phase techniques with Fmoc protecting groups.

CLM What is claimed is:

4. A pharmaceutical composition according to claim 3 wherein said polymer is selected from the group consisting of a **polyethylene glycol**, polypropylene glycol, branched polyethylene imine, polyvinyl pyrrolidone, polylactide, poly(lactide-co-glycolide), polysorbate, **polyethylene oxide**, **poly**(**ethylene oxide**-co-propylene oxide), poly(oxyethylated) glycerol, poly(oxyethylated) sorbitol, poly(oxyethylated glucose), polymethyloxazoline, polyethyloxazoline, polyhydroxyethyloxazoline, polyhydroxypropyloxazoline, polyvinyl alcohol, poly(hydroxyalkylcarboxylic acid), polyhydroxyethyl acrylic acid, polyhydroxypropyl methacrylic acid, polyhydroxyvalerate, polyhydroxybutyrate, polyoxazolidine, polyaspartamide, polysialic acid, linear polypropylene imine, polyethylene sulfide, polypropylene sulfide, polyethylenesulfonate, polypropylenesulfonate, polyethylene sulfone, polyethylenesulfonylethyleneimine, **polycaprolactone**, polypropylene oxide, polyvinylmethylether, polyhydroxyethyl acrylate, polyhydroxypropyl methacrylate, polyphosphazene and derivatives, mixtures and copolymers thereof.

5. A pharmaceutical composition according to claim 4 wherein said polymer is selected from the group consisting of a **polyethylene glycol** and polypropylene glycol and copolymers thereof.

6. A pharmaceutical composition according to claim 5 wherein said polymer is **polyethylene glycol.**

9. A pharmaceutical composition according to claim 8 wherein said anti-cancer agent is selected from the group consisting of paclitaxel, docetaxel, **camptothecin**, and derivatives and analogs thereof.

12. A pharmaceutical composition according to claim 9 wherein said anti-cancer agent is **camptothecin.**

42. A pharmaceutical composition according to claim 41 wherein said peptide comprises a sequence selected from the group consisting of **CRGDC**, CRGDCL, NGR(AHA), DGR(AHA), CRGDCA, RCDVVV, SLIDIP, TIRSVD, KRGD, RRGP and RGDL.

57. A pharmaceutical composition according to claim 56 wherein said polymer is selected from the group consisting of a **polyethylene glycol**, polypropylene glycol, branched polyethylene imine, polyvinyl pyrrolidone, polylactide, poly(lactide-co-glycolide), polysorbate, **polyethylene oxide**, **poly**(**ethylene oxide**-co-propylene oxide), poly(oxyethylated) glycerol, poly(oxyethylated) sorbitol, poly(oxyethylated glucose), polymethyloxazoline, polyethyloxazoline, polyhydroxyethyloxazoline, polyhydroxypropyloxazoline, polyvinyl alcohol, poly(hydroxyalkylcarboxylic acid), polyhydroxyethyl acrylic acid, polyhydroxypropyl methacrylic acid, polyhydroxyvalerate, polyhydroxybutyrate, polyoxazolidine, polyaspartamide, polysialic acid,

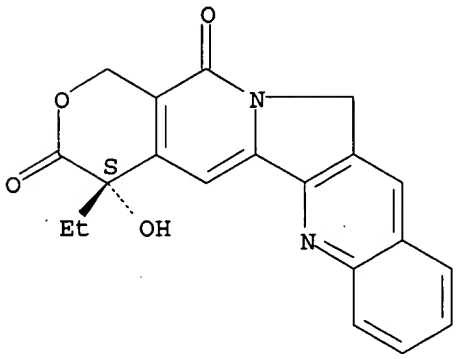
linear polypropylene imine, polyethylene sulfide, polypropylene sulfide, polyethylenesulfonate, polypropylenesulfonate, polyethylene sulfone, polyethylenesulfonylethyleneimine, **polycaprolactone**, polypropylene oxide, polyvinylmethylether, polyhydroxyethyl acrylate, polyhydroxypropyl methacrylate, polyphosphazene and derivatives, mixtures and copolymers thereof.

58. A targeted matrix according to claim 57 wherein said polymer is selected from the group consisting of a **polyethylene glycol** and polypropylene glycol and copolymers thereof.

92. A targeted matrix according to claim 91 wherein said peptide is selected from the group consisting of **CRGDC**, CRGDCL, NGR(AHA), DGR(AHA), CRGDCA, RCDVVV, SLIDIP, TIRSVD, KRGD, RRGP and RGDL.

IT Polymers, biological studies
IT **Polyoxyalkylenes, biological studies**
(targeted delivery systems for bioactive agents)
IT **7689-03-4**, Camptothecin 33069-62-4D, Paclitaxel, conjugates 114977-28-5D, Docetaxel, conjugates
(targeted delivery systems for bioactive agents)
IT 79-10-7D, Acrylic acid, hydroxyalkyl derivative, polymers 79-41-4D, Methacrylic acid, hydroxyalkyl derivative, polymers 9002-89-5, Polyvinyl alcohol 9002-98-6 9003-09-2, Polyvinylmethylether 9003-11-6 9003-39-8, Polyvinylpyrrolidone 9064-17-9, Polypropylene sulfide 9086-85-5, Polyhydroxypropyl methacrylate 24936-67-2, Polyethylene sulfide 24980-34-5, Polyethylene sulfide **24980-41-4**, Polycaprolactone 25037-42-7, Polypropylene imine 25037-97-2, Polypropylene sulfide **25248-42-4**, Polycaprolactone **25322-68-3**, Polyethylene glycol 25322-69-4, Polypropylene glycol 25805-17-8, Polyethyloxazoline 26022-14-0, Polyhydroxyethylacrylate 26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] 26085-02-9, Poly[nitrilo(dichlorophosphoranylidyne)] 26101-52-0 26375-28-0 26680-10-4, Polylactide 26780-50-7, Poly(lactide-co-glycolide) 31694-55-0, Ethoxylated Glycerol 34344-66-6, Polysorbic acid 52352-27-9, Polyhydroxybutyric acid 53694-15-8, Ethoxylated Sorbitol 57118-63-5, Poly(sulfonyl-1,2-ethanediyl) 58548-19-9 61931-73-5, Ethoxylated glucose 102190-94-3, Polyhydroxyvaleric acid 158606-68-9, Polyaspartamide 158820-10-1 206859-46-3 408512-66-3
(targeted delivery systems for bioactive agents)
IT 9087-70-1, BPTI 37231-28-0, Melittin 55068-79-6, Bombinin 72093-21-1, Mastoparan 77752-27-3, Seminal plasmin 80802-79-5, Cecropin 95751-30-7, Charybdotoxin 97762-98-6, Brevinin 108334-53-8, Sarcotoxin 113041-69-3, Magainin 116229-36-8, Bactenecin 123997-21-7, Apidaecin 128906-89-8, Royalisin 131257-09-5, Bombolitin 131889-89-9, Esculentin 133425-01-1, Andropin 136212-91-4, Dermaseptin 138347-64-5 140896-21-5, Indolicidin 146897-68-9, Lactoferricin 148045-74-3, Polyphemusin 148045-87-8, Tachyplesin 149635-29-0 149635-35-8 **153477-08-8** 156476-39-0, β Defensin 159125-12-9 162227-40-9 163663-18-1, Protegrin 179048-25-0, Drosocin 179560-60-2 179560-62-4 179560-63-5 179560-64-6 179560-65-7 184654-51-1, Diptericin 189023-64-1 251460-81-8, α Defensin 408512-69-6 408512-70-9 408512-71-0 408512-72-1 408512-73-2 408512-74-3 408512-75-4 408512-76-5 408512-77-6 408512-78-7 408512-79-8 408512-80-1
(targeted delivery systems for bioactive agents)
IT **7689-03-4**, Camptothecin
(targeted delivery systems for bioactive agents)
RN 7689-03-4 USPATFULL
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione, 4-ethyl-4-hydroxy-, (4S)- (9CI) (CA INDEX NAME)

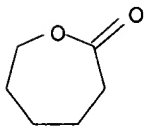
Absolute stereochemistry. Rotation (+).



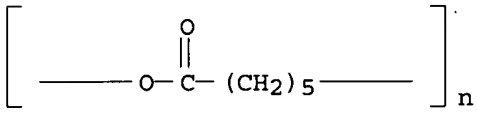
IT **24980-41-4**, Polycaprolactone **25248-42-4**, Polycaprolactone **25322-68-3**, Polyethylene glycol
(targeted delivery systems for bioactive agents)
RN 24980-41-4 USPATFULL
CN 2-Oxepanone, homopolymer (9CI) (CA INDEX NAME)

CM 1

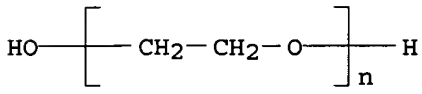
CRN 502-44-3
CMF C6 H10 O2



RN 25248-42-4 USPATFULL
CN Poly[oxy(1-oxo-1,6-hexanediyl)] (9CI) (CA INDEX NAME)

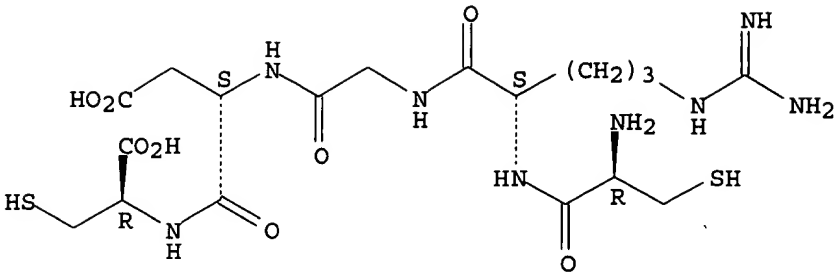


RN 25322-68-3 USPATFULL
CN Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy- (9CI) (CA INDEX NAME)



IT **153477-08-8**
(targeted delivery systems for bioactive agents)
RN 153477-08-8 USPATFULL
CN L-Cysteine, L-cysteinyl-L-arginylglycyl-L-α-aspartyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L143 ANSWER 6 OF 8 USPATFULL on STN
AN 1999:141885 USPATFULL
TI Integrin-binding peptides
IN Ruoslahti, Erkki, Rancho Sante Fe, CA, United States
Koivunen, Erkki, San Diego, CA, United States
PA La Jolla Cancer Research Foundation, San Diego, CA, United States (U.S. corporation)
PI US 5981478 19991109
AI US 1994-286861 19940804 (8)
RLI Continuation-in-part of Ser. No. US 1993-158001, filed on 24 Nov 1993
DT Utility
FS Granted
EXNAM Primary Examiner: Tsang, Cecilia J.; Assistant Examiner: Gupta, Anish
LREP Campbell & Flores LLP
CLMN Number of Claims: 36
ECL Exemplary Claim: 1
DRWN 13 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 1775
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention is directed to novel integrin binding peptides. These peptides bind to α.sub.v - of α.sub.5 -containing integrins and can exhibit high binding affinity. They contain one of the following sequence motifs: RX.sub.1 ETX.sub.2 WX.sub.3 [SEQ ID NO: 1] (especially RRETAWA [SEQ ID NO: 8]); RGDGX [SEQ ID NO: 2], in which X is an amino acid with a hydrophobic, aromatic side chain; the double cyclic CX.sub.1 CRGDCX.sub.2 C [SEQ ID NO: 15]; and RLD. The peptides generally exhibit their highest binding affinity when they assume a conformationally stabilized configuration. This invention also provides methods of using these peptides.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD The cyclic peptides GACRRETAWACGA [SEQ ID NO: 6] (*CRRETAWAC*) [SEQ ID NO: 12] and GA***CRGDC***LGA [SEQ ID NO: 5] (***CRGDC***) [SEQ ID NO: 37] were synthesized using an Applied Biosystems Model 430A synthesizer (Foster City, Calif.) and purified by reverse-phase. . .
DETD . . . hours in the presence of 20 μg/ml of tetracycline, and phage were collected from the supernatant by precipitation twice with **polyethylene glycol.** The phage pellets were dissolved at approximately 10.sup.13 transducing units (TU)/ml in TBS buffer containing 0.02% NaN.sub.3 and stored at. . .
DETD Relative affinities of the CRRETAWAC [SEQ ID NO: 12] and **CRGDC** [SEQ ID NO: 37] peptides were determined by inhibition of binding of peptide-displaying phage to α.sub.5 β.sub.1 integrin. Peptide-displaying phage. . .
DETD . . . 1 hour in the presence of various concentrations of the cyclic peptides containing CRRETAWAC [SEQ ID NO: 12] and containing **CRGDC** [SEQ ID NO: 37] in microliter wells coated with the α.sub.5 β.sub.1 integrin. Binding was quantitated by adding K91kan bacteria. . .

DETD FIG. 4 shows the inhibition of RRETAWA [SEQ ID NO: 8]-displaying phage binding to α.sub.5 β.sub.3 integrin by **CRGDC** [SEQ ID NO: 37] and CRRETAWAC [SEQ ID NO: 12]. The CRRETAWAC [SEQ ID NO: 12] motif inhibited at least 10 times more efficiently than the **CRGDC** [SEQ ID NO: 37] containing peptides. A control peptide GRGESP [SEQ ID NO: 23] had no effect.

DETD . . . 4] phage were added together with various concentrations of the cyclic peptides containing CRRETAWAC [SEQ ID NO: 12] and containing **CRGDC** [SEQ ID NO: 37] into microliter wells coated with the α.sub.5 β.sub.1 integrin, incubated for 1 hour at room temperature and binding to wells was quantitated. As shown in FIG. 2, the CRRETAWAC [SEQ ID NO: 12] and **CRGDC** [SEQ ID NO: 9] inhibit the binding of ELRGDGW-displaying [SEQ ID NO: 4] phage to α.sub.5 β.sub.1 integrin to approximately. . .

DETD The ability of CRRETAWAC [SEQ ID NO: 12] and **CRGDC** [SEQ ID NO: 37] containing peptides to inhibit binding of CRGDCL-displaying [SEQ ID NO: 7] phage to the microwells coated. . .

DETD . . . in FIG. 1, the cyclic CRRETAWAC [SEQ ID NO: 12] peptide inhibits fibronectin binding equally as well as the cyclic **CRGDC** [SEQ ID NO: 37] peptide.

DETD . . . the B2/C1). This attachment was inhibited by the RRETAWA-[SEQ ID NO: 8] containing peptide (1 mM) as well as by **CRGDC** [SEQ ID NO: 8] (1 mM) and by EDTA (10 mM). The α.sub.v β.sub.1 -expressing B2/v7 cells also bound to. . .

DETD A search for high affinity sequences yielded four sequences with the **CRGDC** [SEQ ID NO: 37] motif, each from the CX.sub.7 C library. These sequences contained two additional cysteines, suggesting the presence. . .

DETD . . . ID NO: 34] peptide was 5-fold more active in inhibiting the binding of RGD-displaying phage to α.sub.5 β.sub.1 than the * **CRGDC*** [SEQ ID NO: 37] peptide (FIG. 9). We also synthesized a peptide according to one of the RLD-containing phage. One. . .

DETD . . . disulfide bonding of the peptide. One disulfide bond is possibly formed between the cysteines flanking the RGD sequence, as the ***CRGDC*** [SEQ ID NO: 37] peptide is active. A second disulfide bridge would then form between the CX.sub.7 C cysteines, although. . .

DETD The cyclized ACDCRGDCFCG [SEQ ID NO: 10] peptide was 10-fold more potent than the single disulfide bond-containing peptide ***CRGDC*** [SEQ ID NO: 37] in inhibiting the binding of RGD-containing phage to α.sub.v β.sub.5 (FIG. 10). Phage binding to α.sub.v β.sub.3 was inhibited by the ACDCRGDCFCG [SEQ ID NO: 10] peptide 5-fold better than by ***CRGDC*** [SEQ ID NO: 37], indicating that the ACDCRGDCFCG [SEQ ID NO: 10] peptide binds to both of these α.sub.v integrins.. . .

DETD . . . was low. In α.sub.v β.sub.3 and α.sub.v β.sub.5 binding assays, the peptide had a 100-fold and 1000-fold lower activity than ***CRGDC*** [SEQ ID NO: 37], respectively. The low affinity may partially be due to the tendency of the peptide precipitate at. . .

DETD . . . composed of human α.sub.5 and CHO β.sub.1, with a IC.sub.50 of 6 μM; it was 7-fold more potent than the * **CRGDC** * [SEQ ID NO: 37] (FIG. 11) or *CRRETAWAC* [SEQ ID NO: 12] peptides. Similar results were obtained with MG 63. . . bond-containing ACDCRGDCFCG [SEQ ID NO: 10] peptide had a significantly decreased activity toward α.sub.5 β.sub.1 as compared to the smaller * **CRGDC*** [SEQ ID NO: 37] peptide and was only slightly better than the linear GRGDSP [SEQ ID NO: 21] peptide. We. . .

DETD . . . the peptide inhibited at IC.sub.50 of 0.6 μM and had a 40-fold higher affinity than the single disulfide bond-containing peptides ***CRGDC*** [SEQ ID NO: 37] and A*CRGDGWC*G [SEQ ID NO: 34]. Similar results were obtained with UCLA-P3 cells, where ACDCRGDCFCG [SEQ ID NO: 10] (IC.sub.50 =0.6 μM) showed a 20-fold enhancement in activity relative to ***CRGDC*** [SEQ ID NO: 37]. Dimethyl

sulfoxide at the concentrations corresponding to those added with the peptide had no effect on. . .

DETD . . . IC.sub.50 of 0.2 μM, the peptide was a 20-fold more effective inhibitor of attachment of IMR-90 cells to vitronectin than * **CRGDC*** [SEQ ID NO: 37] (FIG. 13). The RLD-containing cyclic peptide A*CPSRLDSPC*G [SEQ ID NO: 35] showed inhibitory activity only at. . .

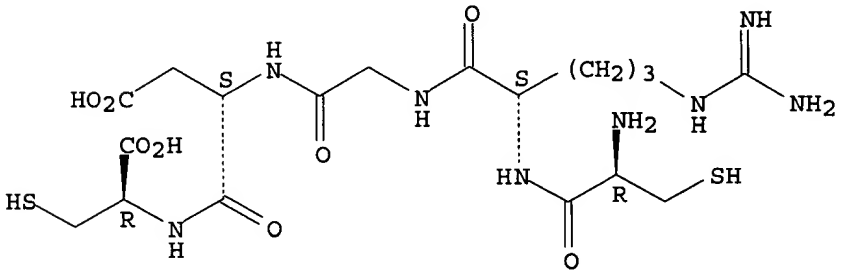
IT 149635-28-9, Gacrgdclga **153477-08-8**, Crgdc 162901-67-9, Acrgdgwcg 162901-68-0, Acdcrgdcfcg 167820-97-5 167820-99-7 167821-01-4 168179-57-5, Cdcrgdcfc 168179-58-6, Cdcrgdclc 168179-59-7, Clcrgdcic 168179-93-9, Rretawa 168179-94-0, Rgdgw 248915-59-5, Gacrretawacga 248915-60-8, Crretawac 248915-61-9, Carrldapc 248915-62-0, Cpsrldspc 248915-63-1, Crsetywkc 248915-64-2 250149-87-2 250149-89-4 250149-91-8 250149-95-2
(integrin-binding peptides and their use in therapy)

IT **153477-08-8**, Crgdc
(integrin-binding peptides and their use in therapy)

RN 153477-08-8 USPATFULL

CN L-Cysteine, L-cysteinyl-L-arginylglycyl-L-α-aspartyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L143 ANSWER 7 OF 8 USPATFULL on STN

AN 1998:157297 USPATFULL

TI Anti-aggregatory peptides

IN Ali, Fadia El-Fehail, Cherry Hill, NJ, United States
Samanen, James, Phoenixville, PA, United States

PA SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)

PI US 5849690 19981215

AI US 1992-918487 19920722 (7)

RLI Division of Ser. No. US 1989-335306, filed on 10 Apr 1989 which is a continuation-in-part of Ser. No. US 1988-191515, filed on 9 May 1988, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Tsang, Cecilia J.; Assistant Examiner: Delaney, Patrick R.

LREP Kinzig, Charles M., Lentz, Edward T.

CLMN Number of Claims: 22

ECL Exemplary Claim: 1

DRWN 7 Drawing Figure(s); 3 Drawing Page(s)

LN.CNT 2535

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to compounds which are effective for inhibiting platelet aggregation, pharmaceutical compositions for effecting such activity, a method for inhibiting platelet aggregation and clot formation in a mammal, and a method for inhibiting reocclusion of a blood vessel following fibrinolytic therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, **polyethylene glycol**, mannitol, sodium chloride or sodium citrate.

DETD . . . buccal administration, the peptides of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or **polyethylene glycols** and molded into a suppository.

DETD . . . ammonium acetate or adipate buffered at pH 3.5 to 5.5. Additional excipients such as polyvinyl pyrrolidone, gelatin, hydroxy cellulose, acacia, **polyethylene**, **glycol**, mannitol and sodium chloride may also be added. Such a composition can be lyophilized.

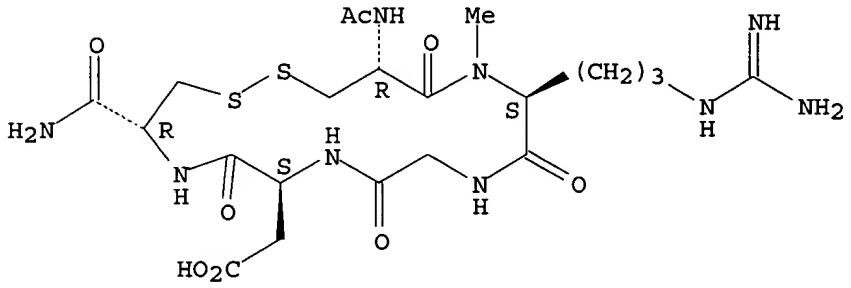
IT 122207-62-9P 123491-66-7P 126053-48-3P 126053-49-4P 126053-50-7P
126053-51-8P 126053-52-9P 126053-53-0P 126053-54-1P 126053-55-2P
126053-56-3P 126053-57-4P 126053-58-5P 126053-59-6P 126053-60-9P
126053-61-0P 126053-62-1P 126053-63-2P 126053-64-3P 126053-65-4P
126053-66-5P 126053-67-6P 126053-68-7P 126053-69-8P
126053-70-1P 126053-71-2P 126053-72-3P 126053-73-4P 126053-74-5P
126053-75-6P 126053-76-7P 126053-77-8P **126053-78-9P**
126053-79-0P 126053-80-3P 126053-81-4P 126053-82-5P 126053-83-6P
126053-84-7P **126053-85-8P** 126053-86-9P 126070-88-0P
126070-89-1P 126070-90-4P 126070-91-5P 126108-83-6P
(preparation of, as blood platelet aggregation inhibitor)

IT **126053-66-5P** **126053-78-9P** **126053-84-7P**
126053-85-8P
(preparation of, as blood platelet aggregation inhibitor)

RN 126053-66-5 USPATFULL

CN L-Cysteinamide, N-acetyl-L-cysteinyl-N2-methyl-L-arginylglycyl-L-α-aspartyl-, cyclic (1→5)-disulfide (9CI) (CA INDEX NAME)

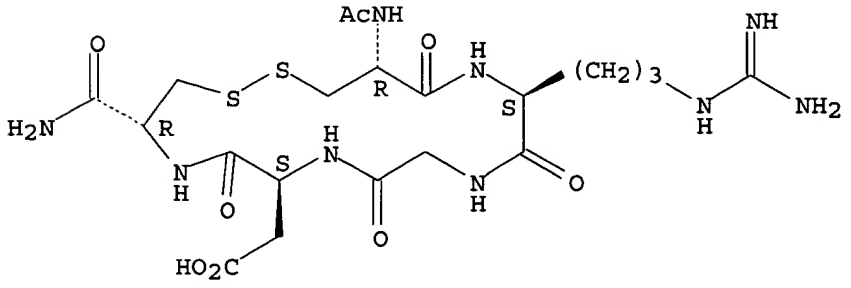
Absolute stereochemistry.



RN 126053-78-9 USPATFULL

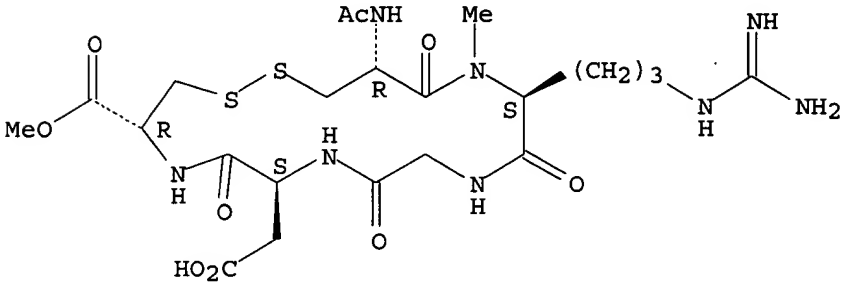
CN L-Cysteinamide, N-acetyl-L-cysteinyl-L-arginylglycyl-L-α-aspartyl-, cyclic (1→5)-disulfide (9CI) (CA INDEX NAME)

Absolute stereochemistry.



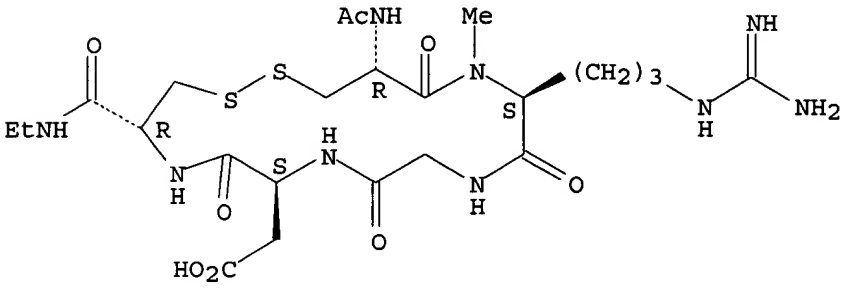
RN 126053-84-7 USPATFULL
CN L-Cysteine, N-acetyl-L-cysteinyl-N2-methyl-L-arginylglycyl-L-α-aspartyl-, 5-methyl ester, cyclic (1→5)-disulfide (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 126053-85-8 USPATFULL
CN L-Cysteinamide, N-acetyl-L-cysteinyl-N2-methyl-L-arginylglycyl-L-α-aspartyl-N-ethyl-, cyclic (1→5)-disulfide (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L143 ANSWER 8 OF 8 USPATFULL on STN
AN 97:56638 USPATFULL
TI Cyclic anti-aggregatory peptides
IN Ali, Fadia El-Fehail, Cherry Hill, NJ, United States
Samanen, James Martin, Phoenixville, PA, United States
PA SmithKline Beecham Corporation, Philadelphia, PA, United States (U.S. corporation)
PI US 5643872 19970701
AI US 1994-296621 19940826 (8)
RLI Continuation of Ser. No. US 1990-630124, filed on 19 Dec 1990, now abandoned which is a continuation-in-part of Ser. No. US 1990-590635, filed on 28 Sep 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-425906, filed on 23 Oct 1989, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Weimar, Elizabeth C.; Assistant Examiner: Marshall, S. G.
LREP Kinzig, Charles M., Lentz, Edward T.
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2973
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to compounds of the formula: ##STR1## wherein: A'

is absent, Asn, Gln, Ala or Abu;

A is absent or a D- or L-amino acid chosen from Arg, HArg, (Me.sub.2)Arg, (Et.sub.2)Arg, Abu, Ala, Gly, His, Lys, or an α-R' substituted derivative thereof, Dtc, Tpr and Pro;

B is a D- or L-amino acid chosen from Arg, HArg, NArg, (Me.sub.2)Arg, (Et.sub.2)Arg and Lys or an α-R' substituted derivative thereof;

Q is absent or a D or L amino acid chosen from Tyr, (Alk)Tyr, Phe, (4'W)Phe, HPhe, Phg, Pro, Trp, His, Ser, (Alk)Ser, Thr, (Alk)Thr, (Alk)Cys, (Alk)Pen, Ala, Val, Nva, Met, Leu, Ile, Nle and Nal, or an α-R' substituted derivative thereof;

M is absent or Gly or a D- or L-amino acid chosen from Glu, Phe, Pro, Lys and Ser or, provided n is 1, B-Gly-Glu-Q;

W is halogen or Alk;

R' is Alk or PhCH.sub.2 ; ##STR2## wherein Z.sub.1 and Z.sub.2 are linked via a covalent bond between L.sup.1 and L.sup.2 ; or Z.sub.1 and Z.sub.2 are, taken together, a covalent bond between the amino terminal residue and the carboxy terminal residue;

L.sup.1 and L.sup.2 are --S-- or --(CH.sub.2).sub.p --;

X is R.sub.4 R.sub.5 N or H;

Y is H, CONR.sub.1 R.sub.2 or CO.sub.2 R.sub.2 ;

R.sub.1 and R.sub.2 are H, Alk or (CH.sub.2).sub.p Ar;

R.sub.3 and R.sub.3' are H, Alk, (CH.sub.2).sub.p Ar or taken together are --(CH.sub.2).sub.4 -- or --(CH.sub.2).sub.5 --;

R.sub.4 is H or Alk;

R.sub.5 is R.sub.11, R.sub.11 CO, R.sub.11 OCO, R.sub.11 OCH(R.sub.11')CO, R.sub.11 NHCH(R.sub.11')CO, R.sub.11 SCH(R.sub.11')CO, R.sub.11 SO.sub.2 or R.sub.11 SO;

R.sub.6 is Alk, OAlk, halogen or X;

R.sub.7 is H, Alk, OAlk, halogen or Y;

R.sub.8 and R.sub.8' are H, Alk, (CH.sub.2).sub.p Ph, (CH.sub.2).sub.p Nph or taken together are --(CH.sub.2).sub.4 -- or --(CH.sub.2).sub.5 --;

R.sub.9 is H, Alk or Y;

R.sub.10 is H or Alk;

R.sub.11 and R.sub.11' are H, C.sub.1-5 alkyl, C.sub.3-7 cycloalkyl, Ar, Ar--C.sub.1-5 alkyl, Ar--C.sub.3-7 cycloalkyl;

Ar is phenyl or phenyl substituted by one or two C.sub.1-5 alkyl, trifluoromethyl, hydroxy, C.sub.1-5 alkoxy or halogen groups;

n is 1 or 2;

q is 0 or 1; and

p is 0, 1, 2 or 3;

or a pharmaceutically acceptable salt thereof;

which are effective for inhibiting platelet aggregation, pharmaceutical compositions for effecting such activity, a method for inhibiting platelet aggregation and clot formation in a mammal, and a method for inhibiting reocclusion of a blood vessel following fibrinolytic therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, **polyethylene glycol**, mannitol, sodium chloride or sodium citrate.

SUMM . . . rectal administration, the peptides of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or **polyethylene glycols** and molded into a suppository.

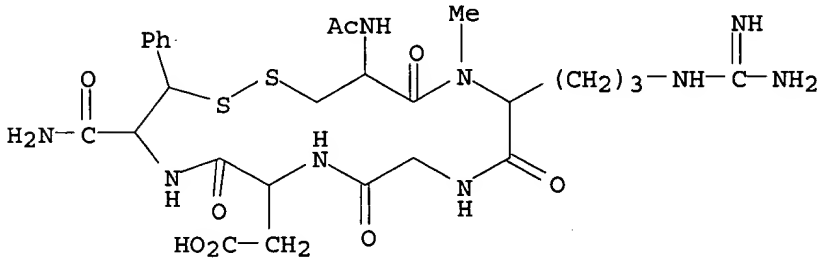
SUMM . . . ammonium acetate or adipate buffered at pH 3.5 to 5.5. Additional excipients such as polyvinyl pyrrolidone, gelatin, hydroxy cellulose, acacia, **polyethylene**, **glycol**, mannitol and sodium chloride may also be added. Such a composition can be lyophilized.

IT 135432-37-0P 136593-89-0P 136593-90-3P 136593-91-4P 136593-92-5P
136593-93-6P 136593-94-7P **136593-95-8P 136593-96-9P**
136593-97-0P 136593-98-1P 136593-99-2P 136594-00-8P 136594-01-9P
136594-02-0P 136594-03-1P 136594-04-2P 136594-05-3P 136594-06-4P
136594-07-5P 136594-08-6P 136594-09-7P 136594-10-0P 136594-11-1P
136620-00-3P 136620-01-4P 136657-53-9P
(preparation of, as antithrombotic)

IT **136593-95-8P 136593-96-9P**
(preparation of, as antithrombotic)

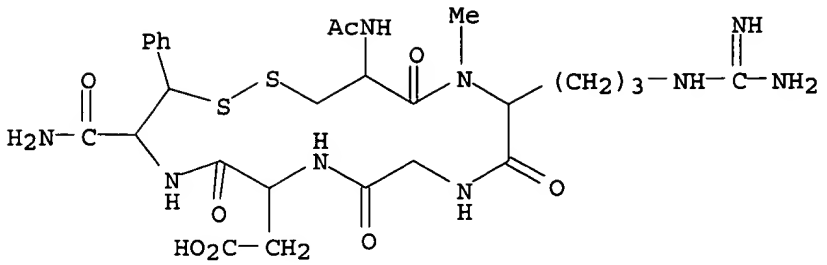
RN 136593-95-8 USPATFULL

CN L-Phenylalaninamide, N-acetyl-L-cysteinyl-N2-methyl-L-arginylglycyl-L-α-aspartyl-β-mercapto-, cyclic (1→5)-disulfide, erythro- (9CI) (CA INDEX NAME)



RN 136593-96-9 USPATFULL

CN L-Phenylalaninamide, N-acetyl-L-cysteinyl-N2-methyl-L-arginylglycyl-L-α-aspartyl-β-mercapto-, cyclic (1→5)-disulfide, threo- (9CI) (CA INDEX NAME)



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=> d his

     (FILE 'HOME' ENTERED AT 06:36:24 ON 22 SEP 2004)
               SET COST OFF

     FILE 'REGISTRY' ENTERED AT 06:36:36 ON 22 SEP 2004
               E CRGDC/SQEP
L1            28 S E3
               E CAMPTOTHECIN/CN
L2             1 S E3
L3            59 S C20H16N2O4/MF AND 5/NR
L4            15 S L3 AND 7726/RID
L5             3 S L4 NOT (LABELED OR (T OR D)/ELS OR 9 HYDROXY)
L6             3 S L2,L5
               SEL RN
L7            10 S E1-E3/CRN
L8             1 S L7 AND NA/ELS
L9             4 S L6,L8
L10            1 S 502-44-3
L11         5603 S 502-44-3/CRN
L12          566 S L11 AND C2H4O
L13           43 S L12 AND 2/NC
L14            6 S L13 AND OC2/ES
               SEL RN 2 4
L15            4 S L14 NOT E4-E5
L16           37 S L13 NOT L14
L17            4 S L16 AND 25322-68-3/CRN
L18            4 S L17 AND 2/NC
               SEL RN 1 2
L19            2 S L18 NOT E6-E7
L20          169 S L12 AND 25322-68-3/CRN NOT L17
L21            1 S L20 AND NA/ELS AND 3/NC
L22          222 S L12 AND 75-21-8/CRN
L23          218 S L22 NOT L13
L24           94 S L23 NOT (N OR S OR P OR SI)/ELS
L25            1 S L11 AND 1/NC
L26            1 S 25248-42-4
L27           25 S 25248-42-4/CRN
L28            1 S L27 AND LI/ELS
L29            1 S L27 AND HEXANOIC
L30            1 S 142-62-1
L31           18 S 142-62-1/CRN AND C2H4O
L32            3 S L31 AND 2/NC
L33            1 S 68993-43-1
L34           93 S 142-62-1/CRN AND PMS/CI
L35            5 S L34 AND 1/NC
L36            1 S 115489-47-9
L37            4 S L25,L26,L28,L36
L38          616 S L11 AND HOMOPOLYMER
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L39          384 S L38 NOT (N OR SI OR S OR P OR CL OR BR OR F OR I)/ELS
L40          174 S L39 NOT (COMPD OR WITH OR UNSPECIFIED)
L41          103 S L40 AND 1/NR
L42            3 S L41 AND SALT
L43            2 S L42 AND LI/ELS
L44            1 S L43 AND 2/NC
L45            5 S L37,L44
L46            1 S 25322-68-3

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L47         2556 S L9
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L49         4401 S L47,L48

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                E 7726/RID
L50         3982 S E82
L51         3978 S L50 NOT L9

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L52         3356 S L51
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L54            7 S CRGDC
L55           23 S ?CRGDC?
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L57            0 S L52 AND L53-L55
L58          216 S L15,L19,L21,L33
L59            0 S L58 AND L56
L60            3 S L58 AND L49,L52
L61            0 S L58 AND L53-L55
L62         7576 S L45
L63         9604 S ?POLYCAPROLACTON? OR POLY CAPROLACTON? OR POLY EPSILON CAPROL
L64        10471 S L62,L63
L65           22 S L64 AND L49,L52
L66            1 S L64 AND L53-L55
L67        76643 S L46
L68        79256 S PEG OR POLYETHYLENEGLYCOL OR POLYETHYELENEOXIDE OR POLYOXYETH
L69          304 S POLY()(ETHYLENEGLYCOL OR ETHYELENEOXIDE)
L70        23999 S POLY()ETHYLENE()(GLYCOL OR OXIDE)
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L72         8093 S POLYOXY ETHYLENE OR POLY()(OXYETHYLENE OR OXY ETHYLENE)
L73       175992 S ETHYLENEGLYCOL OR ETHYLENEOXIDE OR ETHYLENE()(GLYCOL OR OXIDE
L74        67705 S POLYOXYALKYLENE#/CW
L75          249 S L49,L52 AND L67-L74
L76            4 S L53-L55 AND L67-L74
L77           26 S L56,L60,L65,L66,L76
L78           16 S L75 AND L77
L79           26 S L77,L78
                E IMARX/PA,CS
                E IMAR/PA,CS
L80            1 S E16-E19
L81           60 S E43-E66
                E UNGER E/AU
L82          208 S E3,E4,E42-E44
                E MATSUNAGA T/AU
L83          151 S E3,E5
                E MATSUNAGA TERRY/AU
L84           54 S E3-E5
                E RAMASWAMI V/AU
L85           30 S E3,E4
                E ROMANOWSKI M/AU
L86           21 S E3,E5,E6
L87            5 S L80-L86 AND L49,L52
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L89           5 S L87,L88
L90           2 S L89 AND L79
L91           1 S EP98-921109/AP,PRN
L92           6 S L89,L90,L91
L93          24 S L79 NOT L92
L94           4 S L56,L66,L76
                SEL DN AN 3
L95           1 S E1-E3 AND L94
L96           1 S L66 AND L76
L97           6 S L92,L95,L96
L98           3 S L94 NOT L97

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L100          3 S L98 AND L47-L49,L52-L99

     FILE 'HCAPLUS' ENTERED AT 07:28:27 ON 22 SEP 2004
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L102          0 S L101 NOT L99,L100

     FILE 'WPIX' ENTERED AT 07:31:15 ON 22 SEP 2004
L103        822 S L48/BIX
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                E E4+ALL
L104        860 S L103 OR E2
L105          9 S L55/BIX
L106          0 S L104 AND L105
L107       3516 S L63/BIX
                E POLYCAPROLACTONE/DCN
                E POLY CAPROLACTONE/DCN
                E POLY-CAPROLACTONE/DCN
                E POLY(CAPROLACTONE/DCN
                E CAPROLACTONE/DCN
                E E4+ALL
L108       4440 S E2 OR 1294/DRN OR R01295/PLE
L109         19 S L104,L105 AND L107,L108
L110     135530 S L68/BIX OR L69/BIX OR L70/BIX OR L71/BIX OR L72/BIX OR L73/BI
L111       9533 S R02044/DCN OR 2044/DRN
L112      10712 S (A05-H03 OR A05-H03A3 OR A05-H03A4)/MC
L113        126 S L104,L105 AND L110-L112
L114         15 S L109 AND L113
L115          0 S L105 AND L114
L116          1 S L105 AND L109,L113
L117          0 S L104 AND L105
L118          5 S (US20020041898 OR US20040009229)/PN OR (WO2002-US22753 OR US2
                E UNGER E/AU
L119        215 S E3,E4
                E MATSUNAGA T/AU
L120        262 S E3,E4
                E RAMASWAMI V/AU
L121         15 S E3,E4
                E ROMANOSWKI M/AU
                E ROMANOWSKI M/AU
L122          7 S E4
                E IMAR/PA
L123         79 S E53-E60
                E I MARX/PA
L124          4 S L119-L123 AND L104
L125          0 S L119-L123 AND L105
L126         11 S L119-L123 AND L108
L127         55 S L119-L123 AND L110-L112
L128          4 S L124 AND L126,L127
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L129          6 S L116,L118,L128
L130          6 S L129 AND L103-L129

     FILE 'WPIX' ENTERED AT 07:42:46 ON 22 SEP 2004

     FILE 'USPATFULL' ENTERED AT 07:43:26 ON 22 SEP 2004
L131         16 S L1
L132         17 S L54
L133         23 S L131,L132
L134          0 S L133 AND L15,L19,L21,L33
L135          2 S L133 AND L45
L136          3 S L133 AND L63
L137          5 S L133 AND L46
L138          8 S L133 AND L68-L73
L139          5 S L133 AND POLYOXYALKYLENE?/CT
L140          2 S L133 AND L9,L48
L141          0 S L133 AND L51
L142          9 S L135-L140
L143          8 S L142 NOT PACKAGE/TI

     FILE 'USPATFULL' ENTERED AT 07:46:28 ON 22 SEP 2004

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(FILE 'HOME' ENTERED AT 14:38:37 ON 20 SEP 2004)

FILE 'REGISTRY' ENTERED AT 14:39:07 ON 20 SEP 2004
L1 0 S CRGDC
L2 0 S CRGDC/CN
L3 0 S CRGDC
L4 0 S C R G D C
L5 1 S CAMPTOTHECIN/CN
L6 1 S PEG/CN
L7 2 S POLYCAPROLACTONE/CN
L8 0 S CRGDC
L9 4 S CYS ARG GLY ASP CYS

FILE 'CAPLUS, EMBASE, BIOSIS, USPATFULL' ENTERED AT 14:44:24 ON 20 SEP 2004
L10 13274 S L1 OR CAMPTOTHECIN
L11 13467 S L5 OR CAMPTOTHECIN
L12 330953 S L6 OR PEG OR (POLYETHYLENE GLYCOL) OR (POLYETHYLENEGLYCOL)
L13 10616 S POLYCARPOLACTONE OR L7
L14 17 S L9 OR CRGAC
L15 2 S L12 (20W) L13
L16 2035 S L12 AND L13
L17 78 S L11 AND L16
L18 0 S L14 AND L17
L19 47 S L17 AND MATRIX
L20 46 DUPLICATE REMOVE L19 (1 DUPLICATE REMOVED)

=> d l9 1-4
YOU HAVE REQUESTED DATA FROM FILE 'REGISTRY' - CONTINUE? (Y)/N:y

L9 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2004 ACS on STN
RN 646075-27-6 REGISTRY
CN **Peptide, (Cys-Xaa-Cys-Arg-Gly-Asp-Cys-Xaa-Cys) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN 547: PN: WO2004002417 SEQID: 552 claimed protein
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PRP (Properties); USES (Uses)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L9 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2004 ACS on STN
RN 645003-77-6 REGISTRY
CN **Peptide, (Cys-Xaa-Cys-Arg-Gly-Asp-Cys-Xaa-Cys) (9CI)** (CA INDEX NAME)

OTHER NAMES:
CN 439: PN: WO2004002424 SEQID: 552 claimed sequence
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PRP (Properties); USES (Uses)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L9 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2004 ACS on STN
RN 167821-01-4 REGISTRY
CN **Peptide, (Cys-Xaa-Cys-Arg-Gly-Asp-Cys-Xaa-Cys) (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN 5: PN: US5981478 SEQID: 15 claimed protein
CN 62: PN: WO0024782 SEQID: 449 claimed protein
CN 8: PN: WO0181377 SEQID: 14 claimed protein
FS PROTEIN SEQUENCE
DR 250149-93-0, 267652-07-3, 372146-74-2
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PROC (Process); PRP (Properties); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PRP (Properties); USES (Uses)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
4 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L9 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2004 ACS on STN
RN 167820-98-6 REGISTRY
CN **Peptide, (Cys-Arg-Gly-Asp-Cys-Cys-Xaa-Xaa-Cys) (9CI)** (CA INDEX NAME)
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PRP (Properties); USES (Uses)

RELATED SEQUENCES AVAILABLE WITH SEQLINK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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     FILE 'REGISTRY' ENTERED AT 17:06:58 ON 22 SEP 2004
L1             0 S CRGDC
L2             0 S C R G D C
L3             1 S 646075-27-6/RN
L4             1 S 167821-01-4/RN
L5             1 S 167820-98-6/RN
L6             1 S 645003-77-6/RN

     FILE 'CAPLUS, USPATFULL, EMBASE' ENTERED AT 17:10:15 ON 22 SEP 2004
L7            17 S L3 OR L4 OR L5 OR L6
L8            28 S CRGDC
L9            41 S L8 OR L7

     FILE 'REGISTRY' ENTERED AT 17:10:39 ON 22 SEP 2004
L10            1 S CAMPTOTHECIN/CN

     FILE 'USPATFULL, CAPLUS, EMBASE' ENTERED AT 17:10:55 ON 22 SEP 2004
L11         9930 S L10 OR CAMPTOTHECIN
L12            1 S L9 AND L11
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No 102 for the species elected

do 103 ??

L20 ANSWER 25 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2002:276433 CAPLUS
DOCUMENT NUMBER: 136:299693
TITLE: Novel targeted delivery systems for bioactive agents
INVENTOR(S): Unger, Evan C.; Matsunaga, Terry Onichi; Ramaswami, Varadarajan; Romanowski, Marek J.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 46 pp., Cont.-in-part of U.S. Ser. No. 703,474.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002041898	A1	20020411	US 2001-912609	20010725
US 6391687	B1	20020521	US 2000-703474	20001031
WO 2003009881	A2	20030206	WO 2002-US22753	20020718
WO 2003009881	A3	20040408		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004009229	A1	20040115	US 2003-457068	20030605

PRIORITY APPLN. INFO.: US 2000-478124 A2 20000105
US 2000-703474 A2 20001031